

Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei

J Bryant, AJ Clegg, MK Sidhu, H Brodin, P Royle
and P Davidson



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Abstract

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Objectives: This systematic review examines the clinical and cost-effectiveness of the Sugarbaker procedure for treating pseudomyxoma peritonei (PMP) and the costs of the procedure in the UK.

Data sources: Electronic databases, bibliographies of related papers and experts in the field were used as sources for English language studies available up to September 2002.

Review methods: Evidence of the clinical effectiveness of the Sugarbaker procedure for PMP was synthesised through a narrative review with full tabulation of results of all included studies. The economic modelling used a Monte-Carlo simulation model populated with UK price data to estimate likely UK costs.

Results: Five retrospective case-series reports assessing the Sugarbaker procedure met the inclusion criteria for the review, although they were found to be of poor quality when judged against standard criteria for assessing methodological standard. There appears to be some benefit for people with PMP who undergo treatment with the Sugarbaker procedure. Commonly reported complications of the Sugarbaker procedure were anastomotic leaks, fistula formation, wound infection, small bowel perforations/obstructions and pancreatitis. One costing study of poor methodological quality and set in the USA was found. This study, together with UK unit price data and expert advice, was used to populate a Monte-Carlo simulation model to estimate the marginal cost of operating a service to provide treatment for PMP using the Sugarbaker technique rather than standard treatment. The results

of the Monte-Carlo simulation model showed that the cost for one patient over a maximum of 5 years would be about £9700, with a standard deviation of about £1300 (although costs incurred in setting up the specific service or training the staff were not included). The US study showed a ten-fold higher cost. The Monte-Carlo analysis showed that the variation around the mean was not very high. The most likely factor influencing the variation of the costs was the length of procedure. No sensitivity analysis could be done of the alternative treatment.

Conclusions: The economic results should be seen as merely an example of the likely marginal costs of the Sugarbaker procedure, as more information about the current alternative is required. Trained and experienced staff are required to implement the procedure and inevitably time and cost will be involved in developing the appropriate teams. Although the procedure requires some specialist equipment and maintenance, such as smoke evacuators, these should have limited effect on setting up the service. PMP is a relatively rare condition with approximately 50 new cases per year in the UK and the impact of an increase in the demand for services should be limited. Evidence is needed for the effectiveness of maximal cytoreductive surgery compared with surgical debulking, using different intraoperative intraperitoneal chemotherapy strategies, and for the effectiveness of treatments in patients who have residual disease following maximal efforts at cytoreduction. Further research involving high-quality prospective cohort studies with economic evaluations would be valuable.



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List of abbreviations

| | | | |
|--------------|--|-----------|---|
| adj. | adjuvant | MMC | mitomycin C |
| AM | adenomucinosi | MOF-Strep | streptozotocin |
| ANOVA | analysis of variance | MRC | Medical Research Council |
| AWD | alive with disease | MRI | magnetic resonance imaging |
| CC (0/1/2/3) | completeness of cytoreduction score (0 complete, 3 incomplete) | NA | not applicable |
| CEA | carcinoembryonic antigen | NCCHTA | National Coordinating Centre for Health Technology Assessment |
| CR | cytoreduction | NED | no evidence of disease |
| CT | computed tomography | NHS CRD | NHS Centre for Reviews and Dissemination |
| DARE | Database of Abstracts of Reviews of Effectiveness | NHS EED | NHS Economic Evaluations Database |
| DOC | dead of other causes | NSCAG | National Specialist Commissioning Advisory Group |
| DOD | dead of disease | PMCA | peritoneal mucinous carcinomatosis |
| DOT | dead of treatment | PMCA-I/D | peritoneal mucinous carcinomatosis with intermediate or discordant features |
| DPAM | disseminated peritoneal adenomucinosi | PMP | pseudomyxoma peritonei |
| 5-FU | 5-fluorouracil | PSS | prior surgical score |
| HIPEC | hyperthermic intraperitoneal chemotherapy | QALY | quality-adjusted life-year |
| ICD-9 | International Classification of Disease (version 9) | RCT | randomised controlled trial |
| ICU | intensive care unit | SD | standard deviation |
| IPEC | intraperitoneal chemotherapy | | |
| i.v. | intravenously | | |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



Executive summary

Epidemiology and background

Pseudomyxoma peritonei (PMP) refers to a progressive disease process within the peritoneum, thought to originate in the appendix and characterised by the production of copious amounts of mucinous fluid resulting in a 'jelly belly'. If untreated the condition is fatal.

Uncertainty persists as to the specific definition, pathology, site of origin and prognosis of PMP. It is a rare condition, with approximately 50 new cases in England and Wales each year, affecting men and women equally with increased incidence with age. Patients' median survival is approximately 6 years, with 50–70% surviving for 5 years and 10–32% for 10 years. Patients most commonly present with acute appendicitis or increasing abdominal girth. Although there are several treatment options, most patients will undergo either standard treatment of debulking surgery or radical surgery and concomitant perioperative intraperitoneal chemotherapy (IPEC) (Sugarbaker procedure).

Objectives

This systematic review examines the clinical and cost-effectiveness of the Sugarbaker procedure for treating PMP and the costs of the procedure in the UK.

Methods

This report was based on a systematic literature review and modelling of costs.

Data sources

The main electronic databases were searched, with English language limits, for the periods up to September 2002. Bibliographies of related papers were assessed for relevant studies and experts contacted for advice and peer review, and to identify additional published and unpublished references.

Study selection

Studies were included if they fulfilled the following criteria, which were applied by one reviewer and

checked by a second reviewer, with any disagreements resolved through discussion.

- Intervention: (1) traditional surgery debulking resection of all gross disease, (2) cytoreductive surgery combined with chemotherapy or cytoreductive surgery combined with heated adjuvant IPEC (Sugarbaker procedure).
- Participants: people diagnosed as having PMP characterised by histologically benign tumours with indolent course originating in the appendix.
- Outcomes: survival, recurrence or quality of life as primary outcomes and complications as secondary outcome with a minimum of 2 years' follow-up.
- Design: the highest level of evidence available, which was case series. Economic evaluations were included in the review if they included a comparator (or placebo) and both the costs and consequences (outcomes) or if they were costing studies.

Data extraction

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion. The quality of case series was assessed using criteria recommended by the NHS Centre for Reviews and Dissemination (University of York). The quality of economic studies was assessed for their internal validity using a standard checklist, and external validity using a series of relevant questions.

Study synthesis

The clinical effectiveness of the Sugarbaker procedure for PMP was synthesised through a narrative review with full tabulation of results of all included studies. The economic modelling used a Monte-Carlo simulation model, populated UK price data, to estimate likely UK costs.

Results

Number and quality of studies, and direction of evidence

Five retrospective case-series reports assessing the Sugarbaker procedure met the inclusion criteria

for the review. No studies comparing the Sugarbaker procedure with standard treatment, or observational studies of standard treatment were included. When judged using standard criteria for assessing methodological quality, the studies were found to be of poor quality. Patients with different histopathology may have been included in the studies. Details of cytoreductive surgery and chemotherapy differed between studies and not all patients within a series received the same treatment.

Summary of benefits

There appears to be some benefit for people with PMP who undergo treatment with the Sugarbaker procedure. People with PMP have an estimated 5-year and 10-year survival of approximately 50% and 18%, respectively. In contrast, the survival rate of patients following the Sugarbaker procedure is about 90% at 2 years, 60% to about 90% at 3 years, depending on details of IPEC, and 60% to about 68% at 10 years. The percentage of patients with no evidence of disease at the end of follow-up after the Sugarbaker procedure ranged from 41 to 82%. Similarly, the percentage of patients alive with disease at the end of follow-up ranged from 9 to 35%. Mortality due to disease ranged from 2 to 31% in the included studies of the Sugarbaker procedure. Commonly reported complications of the Sugarbaker procedure were anastomotic leaks, fistula formation, wound infection, small bowel perforations/obstructions and pancreatitis.

Costs

No cost-effectiveness or high-quality cost evidence was included in the systematic review. One study of poor methodological quality and set in the USA was found. This study, together with UK unit price data and expert advice, was used to populate a Monte-Carlo simulation model to estimate the marginal cost of operating a service to provide treatment for PMP using the Sugarbaker technique rather than standard treatment. The Monte-Carlo simulation model did not include the costs incurred in setting up the specific service or training the staff. The results of the Monte-Carlo simulation model showed that the cost for one patient over a maximum of 5 years would be about £9700, with a standard deviation of about £1300. The US study showed a ten-fold higher cost. However, the two studies may not be entirely comparable owing to differences in the provision of the specific service and the organisation of the health service.

Cost-utility

No relevant data were available.

Sensitivity analyses

The Monte-Carlo analysis showed that the variation around the mean was not very high. The most likely factor influencing the variation of the costs was the length of procedure. No sensitivity analysis could be done of the alternative treatment.

Conclusions

Limitations of the calculations

The economic results should be seen as merely an example of the likely marginal costs of the Sugarbaker procedure. No policy decision can be made from cost statements without more information about the current alternative. Other questions concerning the capacity and finances of the chosen method have to be left to others.

Implications of Sugarbaker for PMP

If the National Specialist Commissioning Advisory Group were to support the development of additional specialist centres within the NHS, there may be several barriers to implementation. The Sugarbaker procedure requires trained and experienced staff and inevitably there will be the need for a period of training and time costs involved in developing the appropriate teams. Although the procedure requires some specialist equipment and maintenance, such as smoke evacuators, these should have limited effect on setting up the service. PMP is a relatively rare condition with approximately 50 new cases per year in the UK and the impact of an increase in the demand for services should be limited.

Recommendations for research

Evidence is needed for the effectiveness of maximal cytoreductive surgery compared with surgical debulking, using different intraoperative IPEC strategies, and for the effectiveness of treatments in patients who have residual disease following maximal efforts at cytoreduction. Research should take the form of high-quality prospective cohort studies with economic evaluations. Studies should be in histologically homogeneous groups and follow-up should be long enough to assess outcomes such as mortality, survival, recurrence, morbidity, complications and quality of life.

Chapter I

Aim of the review

The aim is to review systematically the clinical effectiveness and cost-effectiveness of the Sugarbaker procedure for the treatment of

pseudomyxoma peritonei (PMP) and to examine the costs of the procedure within the UK setting.

Chapter 2

Background

Description of the underlying health problem

PMP refers to a slowly progressive disease process within the peritoneum that is characterised by the production of copious amounts of mucinous fluid (known as ascites) that gradually fills the peritoneal cavity, resulting in the characteristic ‘jelly belly’.¹

It is thought that PMP originates with an appendiceal adenoma within the appendiceal lumen which continues to grow until it occludes.² When eventually the appendix ruptures, mucus containing epithelial cells from the adenoma slowly leaks out through a process known as disseminated peritoneal adenomucinosis. The perforation may reseal but it is likely to rupture again. Although the primary tumour may change a little in size, epithelial cells will continue to proliferate over several years, seeding the peritoneal cavity with mucus-producing cells and resulting in distinctive peritoneal tumours. It can also extend beyond the peritoneal cavity.

The resulting large quantities of soft, translucent, mucinous material produced within the peritoneum collect over several years at specific predictable abdominal and pelvic sites (e.g. greater and lesser omentum). This is known as the redistribution phenomenon which is determined by the flow and absorption of peritoneal fluid and gravity.^{3,4} Mucinous material is less likely to accumulate initially on intestinal surfaces that are in constant motion by peristalsis. Almost inevitably PMP leads to progressive obliteration of the peritoneal cavity and intestinal obstruction, which is fatal without treatment.³

Uncertainty persists as to the specific definition, pathology, site of origin and prognosis of PMP. The term was originally used to describe mucinous ascites associated with ruptured appendiceal mucoceles, but over time has become broader and is often applied to any condition that causes extensive mucus accumulation within the abdomen and pelvis.³ Studies have included benign and malignant tumours, whether aggressive or not, of the appendix, ovaries, pancreas, gallbladder and bile ducts, stomach, colon, fallopian tubes, uterine corpus, urachus (tube that connects the bladder to

the umbilicus during foetal development, which should close to become a ligament after birth), urinary bladder, breast and lungs.^{2,5} The combination of several different conditions in such a broad ranging definition is thought inappropriate and unhelpful, preventing an understanding of the natural history of PMP and, as a consequence, hindering the development of effective treatment options.

Sugarbaker and colleagues have suggested three prognostically distinct groups, based on tumour pathology:⁶

- disseminated peritoneal adenomucinosis (DPAM), in which tumour cells appear low grade, are relatively scant and do not invade organs or lymph nodes
- peritoneal mucinous carcinoma (PMCA), in which tumour cells are more atypical and may invade the abdominal organs. Lymph-node and liver metastasis remain infrequent
- peritoneal mucinous carcinoma with intermediate or discordant features (PMCA-I/D), which is similar to DPAM but the histology shows features of carcinoma in less than 5% of the histological fields. If more than 5% of the histological fields show carcinoma the diagnosis is PMCA.

They advise that the term PMP syndrome should only be applied to the first of these when the tumour has been determined to emanate from the appendix. This classification of tumours has not been universally adopted. Their analysis suggests that mucinous low-malignant-potential tumours and carcinomas of ovarian origin are pathologically and prognostically distinct and not the cause of PMP. Ovarian tumours are often seen in women with PMP but are thought to represent secondary spread from the appendix.

PMP may present with a variety of symptoms, including nausea, fatigue, abdominal pain, distension or a mass in the abdomen.⁵ The role of imaging, including ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI), in diagnosing PMP appears unclear.² Although non-shifting ascites or CT scans showing abundant material with a density similar to fat

may indicate PMP, diagnosis is usually made at laparotomy for suspected appendicitis or ovarian tumour, or during surgery, when another condition is suspected. Suspected appendicitis is the most common presentation.⁷

Incidence and prevalence

PMP is a rare condition, said to be found at approximately 2 per 10,000 laparotomies.² There are estimated to be 50 new cases in the UK each year, approximately one per million of the population (source: South West Cancer Intelligence Service, based on data from the Pelican Centre, Basingstoke). Men and women are affected equally and the incidence rises with age; half of the cases registered in the South West region between 1990 and 1999 were aged 70 or over (*Table 1*). Mortality from PMP is not recorded because the designated International Classification of Disease, version 9 (ICD-9) code for this condition is not used for underlying cause of death on registers.⁸

PMP has an estimated overall 5-year survival rate of approximately 50–70% and a 10-year survival rate of 10–32%, with a median survival of 5.9–6.25 years.² However, prognosis varies with the nature and origin of the tumour.

It has been reported that up to 76% of patients may develop recurrence of PMP, with 50% of recurrences occurring within 2.5 years.²

Current service provision

The clinical management of PMP depends on the nature of the presentation, subsequent diagnosis and severity of the condition, as well as the

options available for clinical management. Usually patients present with symptoms that may point to other conditions. Abdominal pain, distension or mass in the abdomen, along with more general symptoms of nausea and fatigue, may result in an initial diagnosis of appendicitis or ovarian tumour. Given the initial diagnosis, patients are likely to be referred for treatment to a surgeon or gynaecologist. Usually, patients will undergo a laparotomy, revealing the common features of PMP (outlined in 'Description of the underlying health problem, above'). As a consequence, the diagnosis and clinical management of the patient will need to be re-evaluated. Some patients are diagnosed when undergoing laparoscopy as part of infertility treatment, whereas others may be diagnosed by ultrasonography, CT or MRI. Immediate treatment will depend on the findings at laparotomy or laparoscopy, but may include appendectomy or oophorectomy where possible, together with a generous biopsy, gentle evacuation of mucinous ascites and clearance of any bowel obstruction. Where the primary site is unclear (or seems to be at a site other than the appendix, such as the colon or small intestine), further diagnostic investigations will be required. Establishing an accurate diagnosis underlies effective clinical management as these different conditions require different treatment strategies. When the diagnosis is confirmed through histology, patients will usually undergo either the standard treatment, consisting of debulking surgery undertaken by a local gastrointestinal surgeon, or radical surgery and intraperitoneal and systemic adjuvant chemotherapy (the Sugarbaker procedure) following referral to a specialist centre. Although less likely, patients may undergo other forms of management such as radiotherapy or no active treatment. Recurrence of PMP is common, although the likelihood and frequency depend on the severity of the condition and the knowledge and skill of the responsible surgeon. Further treatment through surgery for recurrent PMP tends to be progressively more difficult, with increasing postoperative morbidity.

Description of interventions considered in this review

Standard debulking surgery

Standard treatment consists of debulking surgery, repeated as necessary, to reduce tumour mass and mucous production.¹ This operation does not aim to remove all tumour but to resect all gross disease to limit the build-up of mucus and the pressure effects of the disease. Although not curative,

TABLE 1 PMP in south-west England, 1990–9

| Age band (year) | No. of cases | Rate/million |
|-----------------|--------------|--------------|
| 35–39 | 1 | 0.2 |
| 40–44 | 2 | 0.5 |
| 45–49 | 0 | 0 |
| 50–54 | 2 | 0.5 |
| 55–59 | 4 | 1.2 |
| 60–64 | 2 | 0.6 |
| 65–69 | 7 | 2.2 |
| 70–74 | 5 | 1.6 |
| 75–79 | 4 | 1.8 |
| 80–84 | 9 | 5.1 |
| 85+ | 2 | 1.4 |
| All ages | 38 | 0.6 |

Source: South West Cancer Intelligence Service.

survival for years is possible with this treatment. As the adenomucinoses tends to be redistributed initially away from the bowel surfaces, possibly as a result of peristalsis, it allows thorough debulking of disease from the parietal peritoneal surfaces without permanent damage to the abdominal structures. The antrum of the stomach, pylorus, ileocaecal valve region, right colon, rectosigmoid colon, pelvic organs and peritoneum can be resected and anastomoses performed. Recurrence of the condition, which depends on the rigour of the initial surgery and possibly the use of adjuvant therapy, requires repeated and progressively more difficult surgery owing to adhesions and fibrosis. Recurrent tumour appears more likely than primary disease to affect the bowel. Tumour removal from the small bowel is difficult and can lead to fistulae and other complications, and excision of a great length of small bowel can lead to malabsorption.

The Sugarbaker procedure

In view of the frequent recurrence of disease and the lack of invasion of the tumour beyond the peritoneum, a more aggressive strategy has been adopted by some clinicians, aiming for cure. This involves more radical surgery and intraperitoneal and systemic adjuvant chemotherapy. The Sugarbaker technique¹ was developed on this basis and consists of:

- maximal surgery: the removal of all tumour deposits by excising the peritoneal surface and some internal organs. This aims to ensure that any residual disease is small enough (<2.5 mm) to be penetrated by cytotoxic agents. Surgery is very extensive, involving dissection of all areas of the abdomen and an average of 2.5 anastomoses (see Appendix 1 for details of peritonectomy procedures)
- maximal chemotherapy applied directly onto any residual tumour: intraperitoneal

chemotherapy (IPEC) agents are instilled into the peritoneum during the operation, before the anastomoses are joined. The surgeon swills the fluid by hand to ensure coverage of all the affected area. Recent developments have focused on the use of heated (40–44°C) intraoperative intraperitoneal chemotherapy (HIPEC). This is thought to improve drug distribution and penetration compared with standard intraperitoneal administration. Further IPEC is administered over the following 5 days.

These techniques may, however, give rise to additional morbidity and mortality.

Uncertainty remains about the mode by which adjuvant chemotherapy should be provided, whether intraperitoneal or systemic. This depends in part on the nature of the condition suffered, but also on the different side-effects and the difficulties in delivering chemotherapy to the site of the tumour. IPEC is thought favourable as it allows high concentrations of chemotherapy to be delivered directly to the site of the tumour on the abdominal and pelvic surfaces.

Treatment for PMP remains controversial, with a wide range of proposed alternatives. Surgical procedures for PMP have continued to evolve. Uncertainty persists as to the clinical effectiveness of the different approaches for managing the condition.

Other treatment options that have been used but which are not considered in the review include: no active treatment; treatment with radiotherapy using isotope implantation; mucolytic agents (such as saline or dextrose) to aid palliative removal of mucus and tumour cell via closed catheter drainage; and phototherapy as an adjuvant to conventional dissection at laparotomy.

Chapter 3

Methods for systematic review and economic evaluation

The a priori methods for systematically reviewing evidence of clinical effectiveness and the economic evaluation were described in the protocol (Appendix 2). Expert comments were obtained from the review advisory group (see Acknowledgements). Although helpful comments were received relating to the general content of the research protocol, none identified specific problems with the methods of the review. Some changes, additions or points of clarification were made to the methods discussed in the original protocol and these are outlined below.

- The importance of distinguishing between the various definitions of PMP used in the assessments of the different interventions was emphasised by the advisory group. It was thought that definitions varied between different cohorts of patients studied and consequently this may determine any comparisons of treatment outcome. To include cases that are a pathologically and prognostically homogeneous group, the definition of PMP used for the review is specifically that characterised by histologically benign peritoneal tumours associated with an appendiceal mucinous adenoma (i.e. disseminated peritoneal adenomucinosis) exhibiting the redistribution phenomenon, with scant cellularity and abundant mucin.
- Although the protocol stated that survival, recurrence, quality of life and complications of the interventions would be assessed to determine clinical effectiveness, it was thought that there should be close scrutiny of evidence of the complications, morbidity and mortality associated with the different procedures.
- Importantly, the systematic review and economic evaluation were undertaken without access to information or advice from the teams providing specialist services to the NHS for patients with PMP in England and Wales. This followed a request from the National Specialist Commissioning Advisory Group (NSCAG), who had asked for the systematic review and economic evaluation. It severely limited the opportunity for understanding the nature of the condition, the services available, the treatment outcomes and costs of the service within the UK setting.

Towards the end of the study, limited access was provided and comments were included.

Sources of information, search terms and a flowchart outlining the identification of studies are described in Appendix 3.

Studies identified by the search strategy were assessed for inclusion through three stages. The titles and abstracts of all identified studies were screened by one reviewer and checked by a second reviewer. The full text of relevant papers was obtained and inclusion criteria applied independently by two reviewers. Data were extracted by one reviewer using a standard data extraction form and checked by a second reviewer. At each stage, any differences in opinion were resolved through discussion. Studies excluded from the review are listed in Appendix 4.

The quality of included case studies was assessed using criteria recommended by NHS Centre for Reviews and Dissemination (NHS CRD, University of York) (Appendix 5).⁹ The quality of any economic evaluations included was assessed using standard checklists for internal validity (Appendix 6). Quality criteria were applied by one reviewer and checked by a second reviewer. Any disagreements were resolved through discussion.

The economic analysis should ideally be done using an established technique for cost-effectiveness or cost-utility analysis to identify policy-related comparison between the Sugarbaker procedure and other current treatment options. A literature search found only one study with explicit cost of treatment information, and in this case no information could be used for costs related to the treatment result. Owing to the lack of statistically verified data the economic part of the study was then limited to a simulation of likely costs based on the information from this study, comments from experts in the USA and UK sources. Unit costs from NHS statistics, judged by economic expertise for this specific case, were used to populate the model. The simulation used a Monte-Carlo technique to simulate a 1000 patient sample, which created the information about the mean cost and also the sensitivity around this mean.

Chapter 4

Clinical effectiveness

Quality, quantity and characteristics of research available

Five retrospective case series reports^{6,10-13} concerning the Sugarbaker procedure met the inclusion criteria for the systematic review and are shown in Appendix 7 and *Table 2*. No studies examining standard debulking surgery met the inclusion criteria for the systematic review.

The quality of these five case series reports was judged using criteria recommended by NHS CRD Report 4 (*Table 2*).⁹ Of the five studies, four^{6,10,12,13} were not based on a representative sample selected from a relevant population and one study (Witkamp¹¹) was unclear. Four^{6,10,12,13} of the five studies did not use explicit a priori inclusion criteria; however, the study by Witkamp¹¹ did. Two studies^{10,11} did not report whether patients entering the study were at a similar point in their disease progression, while three studies^{6,12,13} were unclear. Four studies^{6,10,12,13} were judged unclear

on follow-up length and one study¹¹ did not report follow-up length. All five studies^{6,10-13} were judged to be unclear when reporting whether outcomes were assessed objectively or blinding was used. Of the five studies, four^{6,11-13} were judged as not being applicable to subseries analysis, while Sugarbaker (2001),¹⁰ the one study where subseries analysis was performed, did not provide sufficient description of the series and the distribution of prognostic factors.

The lack of clarity regarding the representativeness of study samples, inclusion criteria, stage of disease progression and follow-up of the studies included in the review makes it difficult to compare the different studies and to assess and compare outcomes.

Participants

A summary of the diagnosis and pathology of participants in the included studies is shown in *Table 3*. Pathological findings indicate that not all patients within the included series meet the inclusion criteria of the review. Results for these

TABLE 2 Comparison of the methodological quality of case series studies using NHS CRD case series quality assessment criteria

| Study | Representative sample | Inclusion criteria | Disease progression | Follow-up | Objective outcomes | Subseries analysis |
|---|-----------------------|--------------------|---------------------|-----------|--------------------|--------------------|
| Ronnett <i>et al.</i> , 2001 ⁶ | × | × | ? | ? | ? | NA |
| Smith <i>et al.</i> , 1992 ¹² | × | × | ? | ? | ? | NA |
| Sugarbaker <i>et al.</i> , 1993 ¹³ | × | × | ? | ? | ? | NA |
| Sugarbaker, 2001 ¹⁰ | × | × | × | ? | ? | × |
| Witkamp <i>et al.</i> , 2001 ¹¹ | ? | ✓ | × | × | ? | NA |

✓, yes; ×, no; ?, unclear; NA, not applicable.

TABLE 3 Participants of included studies

| Study | Participants: clinical diagnosis (n) | Participants: histological/cytological diagnosis (n) |
|---|--|--|
| Ronnett <i>et al.</i> , 2001 ⁶ | PMP or mucinous adenocarcinoma (109) | DPAM (65), PMCA (30), PMCA-I/D (14) |
| Smith <i>et al.</i> , 1992 ¹² | PMP (17) | PMP (17) |
| Sugarbaker <i>et al.</i> , 1993 ¹³ | Peritoneal carcinomatosis from appendiceal cancer (69) | PMP (38) after histology |
| Sugarbaker, 2001 ¹⁰ | PMP (385) | Adenomucinoses (224) and intermediate type/mucinous adenocarcinoma (161) |
| Witkamp <i>et al.</i> , 2001 ¹¹ | PMP (46) | Proven histologically/cytologically no details (46) |

subgroups are therefore not included in the subsequent assessment of effectiveness summary tables, although full details are reported in the data extraction tables in Appendix 7.

Ronnett and colleagues⁶ included all patients ($n = 109$) identified with PMP or mucinous adenocarcinoma with multifocal peritoneal involvement who were surgically treated between 1983 and 1993. Patients were classified into three groups based on their pathology, DPAM, PMCA and PMCA-I/D. Results for the DPAM group only are presented in the summary results of effectiveness as meeting the inclusion criteria for this review.

Smith and colleagues¹² reported on patients ($n = 17$) with clinical and pathological diagnosis of malignant PMP, of known appendiceal origin, treated at Memorial Sloan-Kettering Cancer Center from 1952 to 1989. The study appears to meet the review inclusion criteria, but detailed histology of participants is not given.

Sugarbaker and colleagues¹³ reported results for patients ($n = 69$) with histologically proven peritoneal carcinomatosis from appendiceal cancer, treated between September 1981 and January 1992, of which a subset was confirmed, after surgical review and histopathological findings, to be cases of PMP ($n = 38$). Results for this subset of patients who meet the inclusion criteria of the review are reported in the summary here.

In Sugarbaker's¹⁰ study patients ($n = 385$) with PMP syndrome who received treatment before 1999 were presented. These were later histologically diagnosed as adenomucinosis ($n = 224$) and intermediate-type and mucinous adenocarcinoma ($n = 161$). Results for the adenomucinosis group only are presented in the summary tables in this review.

Witkamp and colleagues¹¹ reported results for medically fit patients ($n = 46$) with technically resectable PMP, who had a cytologically or histologically proven diagnosis and, no sign of distant metastasis on CT of the abdomen and chest, treated at one institute since 1996. Results are presented here in summary tables and as full data extraction, although this study may not be fully comparable to other studies as no pathology details of participants are given.

It is not clear whether any of these studies that have authors in common are effectively multiple publications with overlapping patient groups.

Interventions

The variants of the Sugarbaker procedure used in the five studies are presented in this section of the review.

In the study conducted by Ronnett and colleagues,⁶ all patients were treated in the same fashion by the same surgeon. All patients underwent a series of peritonectomy procedures and organ resections maximally to debulk (cytoreduce) the tumour. In the early postoperative period (days 1–6 postoperation), mitomycin C (MMC) and 5-fluorouracil (5-FU) were instilled into the peritoneal cavity, after which three adjuvant cycles of systemic MMC and intraperitoneal 5-FU were administered.

Smith and colleagues¹² carried out cytoreductive surgery on all patients, and where the appendix could be found it was removed. An omentectomy was also carried out as part of the initial procedure. Of the 17 patients with PMP of appendiceal origin, eight patients underwent multiple debulking for symptomatic recurrence. Ten patients were treated with chemotherapy. Four received IPEC administration, of whom three received fluorodeoxuridine and leucovorin and one received cisplatin. Six patients received intravenous chemotherapeutic administration, of whom three received semustine, 5-FU, vincristine and streptozotocin (MOF-Strep), and one each 5-FU, melphalan and cyclophosphamide. After recurrence of disease, three patients received a second chemotherapeutic regimen.

Sugarbaker and colleagues¹³ carried out cytoreductive surgery, consisting of five peritonectomy procedures: omentectomy–splenectomy, left subdiaphragmatic peritonectomy, right subdiaphragmatic peritonectomy, pelvic peritonectomy–sleeve resection of sigmoid colon and cholecystectomy–lesser omentectomy. Early postoperative IPEC was then carried out using MMC (first preoperative day) and 5-FU (days 2–5 postoperatively). Three additional cycles of delayed intraperitoneal and systemic chemotherapy were given to patients, with 5-FU given intraperitoneally for 5 consecutive days and MMC intravenously on the third day of the cycle.

In the study by Sugarbaker,¹⁰ the overall treatment strategy was described as maximal surgery, involving between one and six peritonectomy procedures (details discussed by the author elsewhere), and followed by maximal perioperative IPEC.

TABLE 4 Table representing outcomes for each case-series report

| Study | Survival | Mortality | Recurrence | Disease status | Complications | Other Outcomes |
|---|----------|-----------|------------|----------------|---------------|---|
| Ronnett <i>et al.</i> , 2001 ⁶ | ✓ | ✓ | × | ✓ | × | × |
| Smith <i>et al.</i> , 1992 ¹² | ✓ | ✓ | × | ✓ | ✓ | ✓ Presenting symptoms ✓ Symptoms duration ✓ Debulking ✓ Reoperations |
| Sugarbaker <i>et al.</i> , 1993 ¹³ | ✓ | × | × | × | × | × |
| Sugarbaker, 2001 ¹⁰ | ✓ | × | × | × | ✓ | × |
| Witkamp <i>et al.</i> , 2001 ¹¹ | ✓ | ✓ | ✓ | ✓ ^a | ✓ | ✓ MMC toxicity ✓ CEA |

✓, yes; ×, no.
^a Calculated by the Southampton Health Technology Assessments Centre reviewers.

TABLE 5 Reporting of follow-up for each case-series study

| Study | Mean follow-up (months) | Median follow-up (months) | Range (months) |
|---|---|--|----------------|
| Ronnett <i>et al.</i> , 2001 ⁶ | 95.7 (DPAM) 27.2 (PMCA) 57.9 (PMCA-I/D) | 104.0 (DPAM) 16.0 (PMCA) 50.5 (PMCA-I/D) | Not reported |
| Smith <i>et al.</i> , 1992 ¹² | 62 | Not reported | 4–120 |
| Sugarbaker <i>et al.</i> , 1993 ¹³ | Not reported | Not reported | Not reported |
| Sugarbaker, 2001 ¹⁰ | 37.6 | Not reported | Not reported |
| Witkamp <i>et al.</i> , 2001 ¹¹ | Not reported | 12 | 1–43 |

Witkamp and colleagues¹¹ reported the results from carrying out aggressive cytoreductive surgery and HIPEC with MMC. Optimal cytoreductive surgery involved removing all visceral and parietal peritoneal surface deposits plus organ removal as necessary, using peritonectomy procedures as illustrated by Sugarbaker (discussed elsewhere). Adjuvant chemotherapy with 5-FU and leucovorin was also given, some 6–12 weeks after discharge, if disease was malignant.

Outcomes

Each of the case series reports a different set of outcomes, as shown in *Table 4*.

All five studies^{6,10–13} reported survival, with three also reporting mortality.^{6,11,12} One study¹¹ reported recurrence. Disease status was reported in two studies,^{6,12} and calculated by the authors of this review from data presented in another study.¹¹ Complications were reported in three studies.^{10–12} Smith and colleagues¹² also reported on presenting symptoms and duration of symptoms, debulking and reoperations, and Witkamp and colleagues¹¹ reported on MMC toxicity and carcinoembryonic antigen (CEA).

Duration

Study duration, or length of follow-up was reported by all but one study,¹³ as shown in *Table 5*. Follow-up was reported as an average value, either mean or median with range. Ronnett and colleagues⁶ reported follow-up for a mean 95.7 and median 104.0 months for DPAM. Smith and colleagues¹² reported a mean follow-up of 62 (4–120) months, with Sugarbaker¹⁰ reporting a mean follow-up of 37.6 months. Witkamp and colleagues¹¹ reported a median follow-up of 12 (1–43) months.

Assessment of effectiveness

Five studies met the inclusion criteria of the review and presented the results of effectiveness of treatment for PMP. Summary details are shown in *Table 6*. Full details are shown in Appendix 7.

Survival

The included studies reported survival at varying time intervals after different treatment regimens.

Two-year survival was reported as 91%¹¹ where treatment was extensive surgical cytoreduction

TABLE 6 Summary of evidence of effectiveness of treatment for PMP

| Study details | Survival | Status/recurrence | Mortality |
|---|---|---|--|
| Ronnett <i>et al.</i> , 2001 ⁶ Design: Case series Intervention: CR + IPEC (MMC and 5-FU) early postoperatively + three cycles of adjuvant systemic MMC and IPEC 5-FU Subjects: PMP (DPAM) N = 65 Follow-up: Mean 95.7 months | 5-year rate: 75% 10-year rate: 68% | NED: 34/65 (52.3%) AWD: 6/65 (9.2%) | DOD: 20/65 (30.8%) DOC: 5/65 (7.7%) |
| Smith <i>et al.</i> , 1992 ¹² Design: Case series Intervention: CR + IPEC (n = 4) and i.v. chemotherapy (n = 6) Subjects: PMP N = 17 Follow-up: Mean 62 (range 4–120) months | 5-year rate: 75% 10-year rate: 60% | NED: 7/17 (41.2%) AWD: 6/17 (35.3%) | DOD: 4/17 (23.5%) |
| Sugarbaker <i>et al.</i> , 1993 ¹³ Design: case series Intervention: CR + IPEC (MMC) + 5-FU Subjects: PMP N = 38 Follow-up: Not known | 3-year rate: 89.5% | NA | NA |
| Sugarbaker, 2001 ¹⁰ Design: Case series Intervention: CR + HIPEC (MMC) Subjects: PMP (adenomucinosis) N = 224 Follow-up: Mean 37.6 months | 3-year rate: 88% adenomucinosis 5-year rate: 86% complete CR and adenomucinosis by pathology | NA | NA |
| Witkamp <i>et al.</i> , 2001 ¹¹ Design: Case series Intervention: CR + HIPEC (MMC) Adjuvant 5-FU and leucovorin if malignant disease Subjects: PMP N = 46 Follow-up: Median 12 (range 1–43) months | 91% at 2 years 81% at 3 years | NED: 32/46 (70%) AWD: 8/46 (17%) Local recurrence: 8/46 (17%) | DOT: 4/46 (9%) DOD: 1/46 (2.2%) DOC: 1/46 (2.2%) Morbidity: 39% |
| CR, cytoreduction; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; DOC, dead of other causes; DOT, dead of treatment. | | | |

plus HIPEC with MMC and adjuvant 5-FU as necessary.

Three-year survival was reported as 81%,¹¹ 89.5%¹³ and 88%.¹⁰ Where extensive cytoreduction plus HIPEC with MMC and adjuvant 5-FU as necessary was used, 3-year survival was 81%.¹¹ In the study reporting the highest 3-year survival rate of 89.5%,¹³ PMP was treated with five peritonectomy cytoreductive procedures followed by IPEC with MMC and postoperative 5-FU. In the study that categorised patients according to histopathology,¹⁰ 3-year survival after treatment with maximal cytoreduction plus HIPEC (MMC) was 88% in cases of adenomucinosis.

Five-year survival was reported in three studies as 75%^{6,12} and 86%¹⁰ after different treatment regimens. In one study⁶ that used a pathological classification system, patients categorised as having DPAM had a 5-year survival rate of 75% after cytoreduction and early IPEC (MMC and 5-FU), followed by three cycles of adjuvant systemic MMC and IPEC 5-FU. A 75% 5-year survival rate was also reported in another study¹² in which all patients had cytoreductive surgery, and some had IPEC and others intravenous chemotherapy. In the third study,¹⁰ a 5-year survival rate of 86% was reported for complete cytoreduction and adenomucinosis by pathology after cytoreductive surgery.

TABLE 7 Morbidity rate and complications due to surgery as reported in included studies

| Study | Complications |
|-------------------------------------|--|
| Smith <i>et al.</i> ¹² | Starch peritonitis (<i>n</i> = 1) |
| Witkamp <i>et al.</i> ¹¹ | Major complications in 18 patients: stomach or bowel perforation (<i>n</i> = 10), enteral fistula (<i>n</i> = 6), pancreatitis (<i>n</i> = 1), pulmonary embolism (<i>n</i> = 3), peripheral pressure neuropathy (<i>n</i> = 5), pneumonia (<i>n</i> = 3), intra-abdominal or wound abscess (<i>n</i> = 4) |

Ten-year survival rates were reported in two studies, as 68%⁶ and 60%.¹² In the study⁶ that used a pathological classification system, patients categorised as having DPAM had a 10-year survival rate of 68% after cytoreduction and early IPEC (MMC and 5-FU) followed by three cycles of adjuvant systemic MMC and IPEC 5-FU. In the study¹² in which all PMP patients had cytoreductive surgery, and some had IPEC and others intravenous chemotherapy, 10-year survival was 60%.

Mortality

Death due to disease was reported as 2% (median follow-up 12 months),¹¹ 24% (mean follow-up 62 months)¹² and 31% (mean follow-up 96 months)⁶ in the studies included in the review that reported this outcome.

Status and recurrence

The percentage of patients reported as disease free at the end of the follow-up period was 41% (mean follow-up 62 months),¹² 52% (mean follow-up 96 months)⁶ and 70% (calculated by review authors) (median follow-up 12 months)¹¹ in the studies meeting the inclusion criteria for the review.

The percentage of patients who were alive with disease was reported as 9% (calculated by review authors) (mean follow-up 96 months),⁶ 17% (median follow-up 12 months)¹¹ and 35% (mean follow-up 62 months).¹²

One study specifically reported recurrences.¹¹ A local recurrence rate (not defined) of 17% was reported.

Complications and morbidity

Two studies^{11,12} reported morbidity resulting from treatment, although the way in which this is reported was not consistent across studies (*Table 7*). The most commonly mentioned complications were anastomatic leaks, fistula formation, wound infection, small bowel obstructions/perforations and pancreatitis. Prolonged ileus requiring parenteral nutrition in one patient was reported in

one study.¹¹ A morbidity rate of 39% was reported in one study.¹¹

One study¹¹ reported toxicity due to chemotherapy. This consisted mainly of problems relating to bone-marrow suppression, with no long-term toxicity observed due to MMC. Adjuvant chemotherapy was discontinued in 18% of patients who received it, owing to intolerable toxicity.¹¹

Clinical experience

It is possible that the clinical experience of those managing patient care may affect the outcome of treatment, particularly where a procedure has continued to be developed and refined. To assess this, studies were grouped into those that included the clinician who has led the development of the Sugarbaker procedure (P. Sugarbaker) (*Table 8*) and those that did not (*Table 9*). A comparison of the results for survival shows much similarity. Results for disease status are less similar although there is much overlap. For the papers where HIPEC was used in addition to cytoreduction, again there is similarity between the Sugarbaker and non-Sugarbaker results for 3-year survival and death due to disease.

It must be noted that the intervention varied between the studies and also within the studies, as not all patients in each series received the same treatment. In addition, little is known about the experience and training of the other teams managing the patients or about other confounding factors that may affect outcomes of treatment.

Summary

- Five retrospective case series considering the Sugarbaker procedure met the inclusion criteria for the review. No studies examining standard debulking surgery were found.
- Quality assessment showed that four studies were not based on a representative sample and one was unclear; four did not use explicit a priori inclusion criteria; two studies did not

TABLE 8 Studies including P. Sugarbaker as a contributor

| Intervention | Survival (%) (years) | | | | Status (%) | | |
|---|----------------------|------|-----------------|----|------------|-----|------|
| | 2 | 3 | 5 | 10 | NED | AWD | DOD |
| CR + IPEC + adj. chemotherapy ^{a6} | | | 75 | 68 | 52.3 | 9.2 | 30.8 |
| CR + IPEC ± late IPEC/i.v. ¹³ | | 89.5 | | | | | |
| CR + HIPEC ^{b10} | | 88 | 86 ^c | | | | 2 |

^a DPAM patients only.
^b Adenomucinosi s patients only.
^c Complete CR + adenomucinosi s.
adj., adjuvant.

TABLE 9 Studies that do not include P. Sugarbaker as a contributor

| Intervention | Survival (%) (years) | | | | Status (%) | | |
|------------------------------------|----------------------|----|----|----|------------|------|------|
| | 2 | 3 | 5 | 10 | NED | AWD | DOD |
| CR ± IPEC or i.v. ¹² | | | 75 | 60 | 41.2 | 35.3 | 23.5 |
| CR + HIPEC ± adj. CT ¹¹ | 91 | 81 | | | 70 | 17 | 2.2 |

^a DPAM patients only.
^b Adenomucinosi s patients only.
^c Complete CR + adenomucinosi s.
adj., adjuvant.

report whether patients were at a similar point in their disease progression, with the remaining studies being unclear; four studies were judged unclear on adequacy of follow-up, with one not reporting length of follow-up; all five studies were judged to be unclear when reporting whether outcomes were assessed objectively or whether blinding was used; the one study with subseries analysis did not provide sufficient description of the series and the distribution of prognostic factors.

- Most of the series were small, with only two including more than 50 patients, and some spanned many years.
- Although all patients had PMP of appendiceal origin, lack of histological detail may mean that different histological subgroups were included.
- Details of cytoreductive surgery and chemotherapy differed between studies and not all patients within a series received the same treatment.
- Each of the case series reported a different set of outcomes, which may include survival rates, mortality, recurrence, disease status and complications.
- Two-year survival rate was reported as 91% for patients treated with cytoreduction and HIPEC with MMC and adjuvant 5-FU as necessary.
- Three-year survival rates were reported as 81% (in a series of patients receiving cytoreduction and HIPEC with or without adjuvant chemotherapy), 88% (in those receiving cytoreduction and HIPEC) and about 90% (in those receiving cytoreduction plus IPEC with or without further IPEC or intravenous chemotherapy).
- Reported 10-year survival rates ranged from 60% (in those treated with cytoreductive surgery with or without either IPEC or intravenous chemotherapy) to 68% (in patients receiving cytoreduction and IPEC and adjuvant systemic chemotherapy).
- In these series of patients with different treatments, the percentage of patients with no evidence of disease at the end of follow-up ranged from 41 to 70%.
- The percentage of patients alive with disease at the end of follow-up ranged from 9 to 35%.
- Mortality due to disease ranged from 2 to 31% in the included studies.
- Surgery was not without complications, although this was not reported consistently across studies. The most commonly reported complications were anastomatic leaks, fistula formation, wound infection, small bowel obstructions/perforations and pancreatitis. Chemotherapy can result in toxicity.

Chapter 5

Economic analysis

Quantity and quality of research on cost-effectiveness of PMP

A literature search was carried out to identify economic studies or costing papers on the Sugarbaker technique for patients with PMP. One paper¹ was identified as having relevant costing information. No economic evaluation papers were found.

One study¹ was found containing explicit cost data for treatment of PMP using the Sugarbaker procedure. Data were gathered from 25 patients with PMP during 1994–1995 who underwent 26 treatments. The median professional fee (including surgery, anaesthesia, intensive care and radiology) was US\$41,004 (range \$13,406–57,626) at 1996 prices. The median hospital charge was reported to have been \$125,918 (range \$59,389–27,838) (it was assumed that the latter figure should be \$127,838). According to the authors this makes a total treatment cost of \$166,000 per patient. In contrast, the same authors in an overview state that the costs for the comparator treatment of traditional general surgery for PMP, with a median survival of 3 years, are \$906,000 (an alleged underestimate) (*Table 10*).

The cost data were low-quality evidence, not coming from a randomised controlled trial (RCT) or comparative observational study. The inclusion and exclusion criteria of the 25 patients were unknown and the costs were charge data, which are generally different from the real cost data needed for this review. It was assumed that a large

part was overhead cost and that insurance companies have paid negotiated list prices. Further, the alternative treatment was based on tentative assumptions concerning the clinical pathway. No justification is given for these assumptions.

Conclusions cannot be drawn about the costs of recent treatments for PMP (e.g. Sugarbaker procedure) or of the alternative to this treatment from this evidence.

Estimating cost-effectiveness of the Sugarbaker procedure for PMP patients in the UK

From an economic perspective treatment of PMP is complex. It includes diagnostic procedures, complicated treatment options and the difficulties associated with long-term secondary consequences of PMP and the primary treatment options. In this study, the primary focus of the economic evaluation was on the use of the Sugarbaker procedure in the clinical management of PMP following diagnosis. Although an attempt was made to describe the resource use associated with the likely follow-up procedures and reoperations, detailed costing was not possible.

Ideally, the study would take a social perspective on variable costs. However, it was not possible to include costs incurred by the patient's family or carers or welfare costs.

This study applied a health technology assessment perspective, which is the question of value for money for compared treatment methods. It did not address the secondary issue of how to finance the chosen method or the costs required to build up capacity either in medical facilities or in the training and development of the professionals or staff needed to provide the service. Thus, the decision whether or not to recommend the Sugarbaker procedure as a clinical and cost-effective intervention was separated from the decision concerning the financing of the service. The latter is more a political than an evidence-based issue.

TABLE 10 Cost for alternative treatment strategy

| | Cost (US\$) |
|--------------------|-------------|
| Laparotomies | 120,000 |
| Chemotherapy | 24,000 |
| Parenteral feeding | 750,000 |
| Hospice care | 12,000 |
| Ileostomy | Unknown |
| Gastrojejunostomy | Unknown |
| Pain management | Unknown |
| Total | 906,000 |

The six major groups of operative procedures that may be used as part of the Sugarbaker procedure are:

- greater omentectomy–splenectomy
- stripping of the left hemidiaphragm
- stripping of the right hemidiaphragm
- cholecystectomy and lesser omentectomy
- antrectomy
- pelvic peritonectomy with resection of rectosigmoid colon.

All of these surgical procedures can be supplemented with intraoperative chemotherapy and (5 days) postoperative intravenous chemotherapy. No evidence is available of a systematic difference between the different forms of chemotherapy treatment. Thus, it is assumed that the economic aspects are the same regardless of the treatment subgroup, irrespective of operative procedure or chemotherapy option.

A policy-orientated economic study needs to investigate a number of issues, for instance:

- What is the current recommended standard procedure, if any, in the UK? Is it the same as that used in the USA? Has there been progress from the historical perspective discussed by Sugarbaker and colleagues?¹
- What is the nature and extent of extra preoperative investigations into the type of operative procedure that should be applied, compared with those needed for the current standard treatment?
- What is the nature and extent of extra preoperative preparations needed before the Sugarbaker procedure that are different from the current standard procedure?
- Are the follow-up procedures different for the Sugarbaker procedure than for the current standard procedure?

This study estimated costs for the Sugarbaker procedure in terms of (1) the number of professionals involved and their status, (2) the type of equipment used, and (3) the time used in the operating theatre. The study assumed some cost for the operating theatre itself as a capacity price (if free capacity is at hand basically there is no need to estimate any cost of the operating space). The time in postoperative treatment and that spent in the intensive care unit (ICU) should be registered and costed at variable costs. Ward costs may be approximated by the variable day-care cost if the patients can be judged to draw an average resource consumption. Otherwise, compensation

should be made to maintain the marginal cost perspective. The amount of chemotherapy used should be costed according to the pharmacy cost, but should also include (1) possible preparation outside pharmacy, (2) staff monitoring of administration into the body, and (3) follow-up of the results. If drugs are not given in an ordinary hospital setting but in day care or home care, which appears unlikely, this should be costed separately. Follow-up is done every 3 months (tumour markers) and 6 months (CT scan). It should be checked how long this follow-up lasts. It should be checked whether reoperations follow the same procedure as the first one or whether other procedures, staff, equipment or time are used. Finally, various complications may arise as a result of the disease itself or the treatment. Such complications, either short term or long term, should be recognised and costed.

As the different kinds of activity above were defined and quantified, unit prices were investigated according to the following priority order:

1. existing variable unit costs for defined procedures in the NHS system collected for health technology assessment purposes
2. existing unit costs from previous studies, NHS registers or other registers collected for other purposes
3. assumptions about costs taken from similar studies or registers, or from (subjective) expert opinion. Such assumptions should be motivated and supplied with at least simple one-dimensional sensitivity analysis.

Economic model

An economic model can serve as an alternative to prospective randomised data to give some information of the expected cost of treatment in the UK. However, little or no literature was found regarding costs for the Sugarbaker or alternative procedures. As such, the model was developed to be as simple as possible, reflecting the type of information presented by Sugarbaker and colleagues.¹ Unfortunately, there is limited evidence concerning the differences in the epidemiology of PMP between England and Wales and the USA, limiting any comparison. An extensive investigation would be needed to obtain these data.

The economic model concentrated on the following basic issues:

- What is the likely operating time in the operating theatre for a PMP?

- How many surgeons are present?
- How many anaesthesiologists are present?
- How many nurses are present at the operation?
- Is any special equipment necessary that would not generally be used?
- What time is spent in intensive care (hours)?
- How long does the patient spend on the ward (days)?
- How long does the patient spend recovering at home (days)?
- If the patient undergoes reoperation, is it a similar procedure to before?

Follow-up

- Outpatient/inpatient?
- Time lost for patient (hours)?
- Expensive equipment, e.g. scanner?

Information concerning the current standard procedure for PMP was considered to be of poor quality and was excluded from the study.

With the use of data of this kind rough cost estimates were made using estimated unit prices from a local NHS hospital trust for operating theatre time, surgery ward day-care cost and other costs. Time loss for patients can be estimated from the literature. A Monte-Carlo analysis was used to judge the likely variation around given mean values for the different cost estimates.

Initial PMP procedure data

Only one published study could be used for an assessment of the cost for this procedure,¹ which was not detailed enough for assessing cost from a health technology assessment point of view. Additional background information was sought for this study, but little was found. However, an expert in the USA provided data from personal experience (Sugarbaker PH: personal communication, 2002). This information was used with guidance from expert advisors concerning variations between the USA and the UK.

Thus, since no published health technology assessment orientated economic evidence was available, a Monte-Carlo simulation model was designed using assumptions from published studies and personal communications:

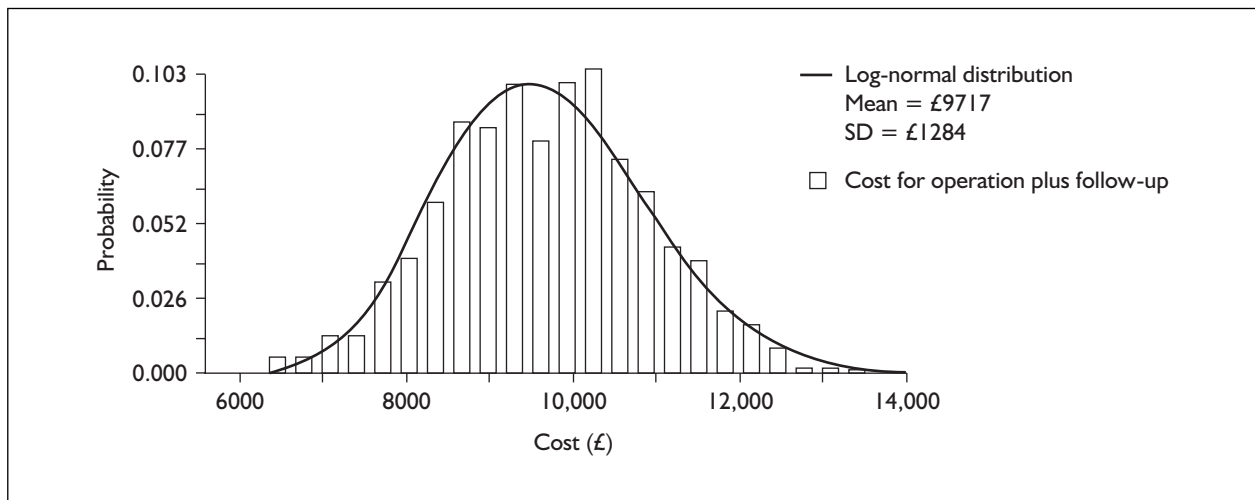
- Operating time was given to be 10.1 ± 2 hours (range 6–17 hours). It was assumed that the frequency distribution is log-normal with the above specifications. Special equipment, not used in other treatments, was assumed to cost £200 per operation.

- It was assumed that 50% of patients would stay in the ICU for 24 ± 36 hours. Another 5% would need long-term respiratory support. After comments from UK experts, it was assumed that 95% of all patients would go to the ICU for (assuming a log-normal distribution) a mean of 24 hours and SD of 3.5 hours (range 15.4–36.7 hours). The remaining 5% would stay in the ICU for 1 week. As an alternative, the cost if all patients stay in the ICU for 1 week was also estimated.
- A patient's stay in a surgical ward was given to be 21 ± 5 days. It was assumed that this information is normally distributed with a range between 6 and 36 days.
- Patients will have outpatient follow-up visits every 3 months for 5 years. The overall 5-year survival is about 60%. Therefore, it was assumed that 40% will have died during the 5 years (following a rectilinear mathematical function), affecting the actual number of visits made. Discounting of costs was done using a 5% discount rate.
- Two trained surgeons, one consultant and one registrar would be present for the entire operation.
- One consultant anaesthetist would be present 30 minutes before the operation plus during the entire operation.
- At least two trained nurses (grade E) and an auxiliary nurse (grade A) would be present during the entire operation.
- A special non-staff cost was added to cover running costs of the operating theatre and equipment. Special equipment such as a smoke evaporator and a self-retaining retractor, as well as the chemotherapeutic agent (MMC), were not costed. The equipment for heating MMC was set at £200 per operation (Moran B: personal communication, 2002).
- Recovery at home, whether NHS costs (GP or nursing costs) or costs to the patient or carers, was not explicitly costed.
- Reoperation was stated to have to be done for 25% of patients. This cost was added to the first operation with the same statistical distribution.
- A follow-up CT scan was included in every second visit.

Because of the scope of, and the limitations placed on the study, the model of the Sugarbaker procedure for PMP was simplified. As a consequence, certain items were costed as an aggregate cost. For example, the pharmaceutical cost of chemotherapy was incorporated in the overall cost of the theatre costs and not specified as a separate cost. Importantly, the cost of preparing

TABLE 11 Expected statistical treatment cost per patient

| Activity | Cost per patient | SD |
|---|------------------|--------------|
| Surgeon cost at operation | £642 | £120 |
| Anaesthiologist cost at operation | £349 | £64 |
| Two trained nurses | £228 | £43 |
| One auxiliary nurse | £62 | £12 |
| Operating theatre cost | £628 | £117 |
| Special equipment cost | £200 | 0 |
| Total operation cost | £2108 | £355 |
| Patients to ICU, short-term cost | £1071 | £146 |
| Patients to ICU, long term cost | £394 | 0 |
| Hospital ward (days) cost | £3251 | £762 |
| Recovery (welfare) cost in home (days) | Unknown | |
| Reoperation cost | £1706 | £215 |
| Total hospitalisation cost | £8531 | £1075 |
| Follow-up outpatient cost | £930 | £556 |
| CT scan | £256 | £153 |
| Total follow-up cost | £1186 | £710 |
| Total treatment cost per statistical patient | £9717 | £1284 |

**FIGURE 1** Frequency distribution around the expected value of total costs

and administering the chemotherapy was included in the general nursing cost at operation.

Simulation results

The model was used to generate a forecast of 1000 treated patients using the characteristics above. Some were predicted to have a short operation time, others a long operation time. Some will have a short hospitalisation time, others a long hospitalisation time. Some were programmed to survive for the entire 5 years, others for only the initial hospital period. All patients used the staff and other resource costs stated in the assumptions above.

All simulated patients were compiled into a set of cost forecasts adding up to an expected cost per patient (Table 11).

The variation around the expected value according to the assumptions can be seen in Figure 1, together with a fitted log-normal distribution. The log-normal fit is not very accurate. There seem to be two cost tops, which may be due to the simplified assumptions of short- and long-term ICU care. Other frequency distributions could be tried, but would give no further information about the likely distribution of costs.

The cost per patient given by the study by Sugarbaker and colleagues¹ was US\$166,922, with minimum and maximum costs of US\$72,795 and \$185,464, respectively. In 2001 UK values this corresponds to £145,146, minimum £63,298 and maximum £161,269. The present data show a radically different view: about one-tenth of this cost. There may be several reasons for this, such as lower salary levels or the difference between the UK tax-funded health system and the insurance-based system in the USA. One important reason may also be that the US study used charges as a measure of costs, which is rarely a correct measure for the purposes of health technology assessment. Charges always include different and additional administrative items, which are not part of the real resource use. Finally, the model could be misspecified in variables, quantities or values. Data were obtained both from current standard treatment and from the Sugarbaker procedure, but they may be biased for the following reasons: subjective data source, the patients may be selected, the US resource use is probably different to the UK, the US organisation is different to the UK (NHS vs insurance) and UK detailed knowledge was not available to the reviewers.

The present Monte-Carlo simulation may also be sensitive to different assumptions, but according to the model specification the factor most likely to change the results of the model is the operation time. However, variations in operation time would probably not change costs ten-fold. Another important assumption is the time spent in the ICU. If it were assumed that all patients spend 1 week in the ICU, the cost per patient would be almost £7000 higher.

The comparative costs, how PMP patients are treated if they do not receive the Sugarbaker procedure, are very difficult to specify without careful investigation. Only the brief statements from the study by Sugarbaker and colleagues in 1996 were published, and they cannot be used for a cost-effectiveness analysis. The reviewers refrain from this comparison.

Different kinds of complication may arise as a result of the disease itself or the treatment. These complications may also be different depending on whether the Sugarbaker procedure or another

procedure is used. There was no possibility to investigate these costs.

Before any policy recommendations could be made from the economic viewpoint, information about the different treatments currently used for PMP would be needed. In addition, the Sugarbaker procedure should be compared in an RCT study or a well-designed observational study so that the extra resource use could be compared with the outcomes in terms of survival and quality of life. Medium-term (2–5 years) outcomes and cost should also be investigated.

Summary

- No economic evaluations were found.
- One US costing study was identified which reported the total cost of PMP treatment as \$166,922 (range \$72,795–185,464). In 2001 UK values this corresponds to £145,146 (£63,298–£161,269).
- In the absence of relevant literature and data from RCTs, a simple economic model using Monte-Carlo simulation was developed. The American study, expert advice and UK unit price data were used to populate the model.
- Results from the model suggest that total treatment cost per patient might be about £9700 (SD £1300). This contrasts radically with the study from the USA, being about one-tenth of their results; however, the studies may not be entirely comparable, owing to their different settings.
- The Monte-Carlo simulation may be sensitive to the assumptions used in the model specification. However, the factor most likely to change the results of the model is the operating time and this is unlikely to change costs by a ten-fold factor. Time spent in the ICU is another important assumption, and if all patients (as opposed to 5%) had a 1-week stay, the cost per patient would be about £7000 higher.
- The economic results are limited to likely costs of the Sugarbaker procedure for PMP and cannot be used for policy recommendations.
- Further study is needed to assess extra resource use of this procedure and outcomes in terms of quality of life to allow cost-effectiveness evaluations.

Chapter 6

Implications for other parties

The Sugarbaker procedure for the treatment of PMP is an invasive therapy which may require hospitalisation for some weeks and long-term recuperation. This will have an impact on the family and other carers, especially if treatment

occurs in a distant specialist centre. Following discharge from hospital, the patient will require continued support at home from primary care and social services, including enteral and parenteral nutrition, rehabilitation and home help services.

Chapter 7

Factors relevant to the NHS

If it were decided to support the development of additional specialist centres within the NHS, there may be several barriers to implementation. The Sugarbaker procedure requires trained and experienced staff and inevitably there will be the need for a period of training, with the consequent time costs involved in developing the appropriate teams. A team should include a consultant surgeon, a senior registrar, an experienced anaesthetist, a specialist nurse, and other nursing and ancillary staff. In addition to training, teams need to be involved in performing the procedure on a regular basis to maintain their skill level. Although the procedure requires some specialist

equipment and maintenance, such as smoke evacuators, these should have a limited effect on setting up the service. Expert opinion has suggested that patients with PMP undergoing treatment with the Sugarbaker procedure place heavy demands on the ICU/high dependency unit, necessitating protected capacity. Exposure to low-dose intraoperative chemotherapy by health workers, by inhalation, contact, ingestion and injection will need consideration. PMP is a relatively rare condition with approximately 50 new cases per year in the UK and the impact of an increase in the demand for services should be limited.

Chapter 8

Discussion

Statement of principal findings

The main findings of this review of the Sugarbaker procedure for the treatment of PMP are summarised below.

The evidence of effectiveness comes from a small number of poor-quality retrospective case series. Details of cytoreductive surgery and chemotherapy differed between studies and not all patients within a series received the same treatment. The 2-year survival rate is about 90%, 3-year survival rates range from 60% to about 90% depending on details of IPEC, and reported 10-year survival rates range from 60% to about 68%. The percentage of patients with no evidence of disease at the end of follow-up ranged from 41 to 82%. The percentage of patients alive with disease at the end of follow-up ranged from 9 to 35%. Mortality due to disease ranged from 2 to 31% in the included studies. Commonly reported complications of surgery were anastomatic leaks, fistula formation, wound infection, small bowel perforations/obstructions and pancreatitis.

The cost per patient given by the 1996 study was \$166,922, with minimum and maximum costs of \$72,795 and \$185,464, respectively. In 2001 UK values this would correspond to £145,146, minimum £63,298 and maximum £161,269. The present data show a radically different view, less than one-tenth of this cost, £9700. There may be several reasons for this, the most important probably being differences in the perception and definition of resource use. The present study used a health technology assessment-based cost concept, which is more compliant to an opportunity cost perspective than accountancy charges. The model could be misspecified in variables, quantities or values, since it was based on one source. With limited information provided about the study design and being set in the USA, it is unlikely to be generalisable to the UK.

The present Monte-Carlo simulation may also be sensitive to different assumptions, but according to the model specification the factor most likely to change the results of the model is the operation time. However, this would not change costs by a factor of ten.

A cost-effectiveness study was not undertaken owing to the limited information available on the Sugarbaker procedure and alternative treatment options.

Strengths and limitations of the review

The systematic review has certain strengths, including the following:

- The systematic review is independent of any vested interests.
- The systematic review brings together the evidence for the effectiveness of the Sugarbaker procedure for the treatment of PMP and an economic evaluation applying consistent methods of critical appraisal and presentation.
- The review was guided by the principles for undertaking systematic reviews as outlined in NHS CRD Report 4 (2nd edition).
- Before undertaking the review the methods of the review were set out in a research protocol (Appendix 2), which was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods used to undertake the different stages of the review.
- An advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.

In contrast, there were certain limitations placed on the review.

- Because of time constraints placed on the review there was a lack of follow-up with authors of studies to clarify methodological details and results from the primary studies.
- The review was limited to including published studies. Abstracts and conference proceedings were excluded from the study as these often fail to provide adequate details of the methods of the study and their results.
- The systematic review and economic evaluation were undertaken without access to information or advice from the teams providing specialist

services to the NHS for patients with PMP in England and Wales, following a request from NSCAG. This severely limited the opportunity for understanding the nature of the condition, the services available (structure and resources used), the treatment outcomes and costs of the service within England and Wales. Towards the end of the study limited access was provided and comments have been included.

Other issues

Difficulties exist with the definition of PMP. It is a term that has been broadly applied and includes a heterogeneous group of pathological lesions. Different pathological definitions are used to diagnose the same morphology, with little consensus on whether PMP should be classified as a malignant condition or not, and on the point of separation between PMP and carcinomatosis peritonei due to high-grade mucinous carcinoma. This review has tried to include groups of patients who are histologically and prognostically similar by applying the narrow definition of PMP as DPAM and excluding peritoneal carcinomatosis and hybrid variants. A number of studies identified during the review included patients with different pathological subtypes, such as pseudomyxoma/adenocarcinoma variant and mucinous carcinoma, in addition to those with disseminated peritoneal adenomucinosis, but as results were not presented for each subgroup, these studies had to be excluded.

The literature relating to PMP is limited. PMP is a rare condition and as such the study of PMP consists of only a few small studies and there are no RCTs. Evidence was limited to case series of the Sugarbaker procedure only and no studies of standard debulking surgery were found.

The published studies that have been included in the review are retrospective case series of generally poor quality when judged using criteria recommended by NHS CRD, considering factors of representativeness of study samples, inclusion criteria, disease state, follow-up and use of objective outcomes.

Within the studies included in the review patients are at different points in the disease process and receive different treatment in terms of procedures to obtain maximal cytoreduction, and different courses of chemotherapy in terms of route and timing. Some have already received treatment for PMP, often at another institution, which makes it

difficult to assess the impact of current treatment. Some studies have spanned decades, during which time surgical procedures will have evolved. With recurrence of PMP repeated surgery is more demanding, with a consequent impact on results.

There are problems associated with length of follow-up. In most studies the length of follow-up may have been inadequate for all important events to occur for all patients. Often details of the study methodology are not clear. In particular, no rationale is provided in defining the start and end-points of follow-up for the different cohorts of patients. Differences in defining follow-up may impact on the assessment of outcomes and increase uncertainty about the comparability of different studies.

In addition to the problems in quantity and quality of research, the quality of reporting of studies is poor. Problems range from lack of clarity and explicitness making interpretation difficult (e.g. several pathological definitions used in the same text; not always possible to follow through patient numbers) to omissions of information (e.g. no details of patient representativeness; no supporting group data, only graphs; reanalysis by histological subtype with no original data; data just reported in abstracts and not in the text; conclusions drawn with no supporting data).

Problems exist with the use of outcomes such as completeness of cytoreduction, recurrence and status. Complete cytoreduction has been defined as residual deposits of tumour less than 2.5 mm in size, so even with complete cytoreduction some small nodules remain which can then progress. Therefore, it is not always clear when recurrence is really recurrence or just persistent progressive disease after complete cytoreduction. As such, information on patients AWD may be more informative than reported recurrence of disease if the amount of residual disease after surgery is not clear.

The results suggest that some histological subgroups may have better survival after aggressive cytoreduction and chemotherapy than others, although results are not conclusive. For PMCA and PMCA-I/D, 5-year and 10-year survival rates are reported as being less than those for DPAM.⁶ Survival at 3 years by histology is less for hybrid adenomucinosis and mucinous adenocarcinoma than for adenomucinosis.¹⁰ Data for these subgroups come from just two studies included in the review.

Radiology, such as CT scanning, is becoming widely used to establish the preoperative diagnosis and extent of PMP due to the characteristic redistribution phenomenon. Differential diagnosis from peritoneal carcinomatosis, by CT appearance and histological analysis at the time of operation, may have an impact on treatment by allowing the prediction of who might be cytoreduced and the selection of patients for aggressive management with curative intent. It has been suggested that inappropriate early debulking surgery before differential diagnosis may result in tumour cell entrapment and consequently may have a detrimental effect on the success of later specialised cytoreductive surgery.

Expert opinion suggests that early diagnosis and consequently early referral for treatment have the potential to affect outcomes. This has consequences for developing appropriate diagnostic services as well as specialist referral centres.

Implications for research

In undertaking the systematic review, certain implications for research have become evident. These include the following.

Evidence is needed for the effectiveness of maximal cytoreductive surgery compared with standard debulking using different adjuvant treatments and the effectiveness of treatments in patients who have residual disease following maximal efforts at cytoreduction. Research should take the form of high-quality prospective cohort studies with economic evaluations. Studies should be in histologically homogeneous groups and follow-up should be long enough to assess outcomes such as mortality, survival, recurrence, morbidity, complications, quality of life and process of care aspects. In addition, the economic evaluation should compare the differential resource use and the outcomes of care (i.e. mortality and quality of life).



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Contributions of authors

A Clegg (Senior Research Fellow) contributed to writing the protocol, determining the inclusion criteria and drafting the report. P Royle (Senior Researcher) contributed to data searching and drafting the report. J Bryant (Senior Researcher) contributed to determining the inclusion criteria, data extraction and drafting the report. M Sidhu (Research Fellow) contributed to determining the inclusion criteria, data extraction, economic evaluation and drafting the report. H Brodin (Senior Research Fellow) contributed to determining the inclusion criteria and economic evaluation. P Davidson (Senior Lecturer/Specialist Registrar in Public Health) contributed to drafting the report in public health.



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13. Sugarbaker PH, Zhu BW, Sese GB, Shmookler B. Peritoneal carcinomatosis from appendiceal cancer: results in 69 patients treated by cytoreductive surgery and intraperitoneal chemotherapy. *Dis Colon Rectum* 1993;**36**:323–9.

Appendix I

Peritonectomy procedures and intraperitoneal chemotherapy details

The objective of cytoreductive surgery is to remove all clinical evidence of disease. This involves a series of peritonectomy procedures to strip the parietal peritoneum and resect structures at fixed sites that contain peritoneum to accomplish a complete cytoreduction. Six peritonectomy procedures are performed as necessary to make the abdomen free of disease:¹

- greater omentectomy–splenectomy
- stripping of the left hemidiaphragm
- stripping of the right hemidiaphragm
- cholecystectomy and lesser omentectomy
- antrectomy
- pelvic peritonectomy with resection of the rectosigmoid colon.

Peritoneal adenomucinosis can be stripped from the parietal peritoneal surface using laser mode electro-surgery. A ball-tipped electro-surgical handpiece is used for direct evaporation of mucinous tumour and also for dissection.

HIPEC is initiated after resection of tumour and MMC, heated to 40–44°C, is instilled in peritoneal

dialysis solution via a Tenckhoff catheter. Continuous manipulation of all viscera by the surgeon's hand over a period of 90 minutes ensures that all surfaces have uniform exposure to chemotherapy.

The benefits of HIPEC are as follows.

- Heat increases drug penetration.
- Heat increases the cytotoxicity of selected chemotherapy agents.
- Heat has antitumour effects.
- Intraoperative chemotherapy allows manual distribution of the drug and heat uniformly to all surfaces of the abdomen and pelvis.
- Nausea and vomiting are avoided because the patient is under anaesthesia.

IPEC may be continued for 5 days postoperatively, usually with 5-FU. Additional cycles of intraperitoneal and systemic chemotherapy may be used.

Appendix 2

Rapid and systematic review methods from the research protocol

Research question

To undertake a systematic review of the clinical effectiveness and costs of the Sugarbaker procedure for the treatment of PMP.

Clarification of research question and scope

The aim is to provide a systematic review to assess the effects of the Sugarbaker procedure (maximal surgery plus maximal chemotherapy) for the treatment of non-malignant PMP of appendiceal origin.

The review will be from the perspective of the NHS and PSS regarding costs and the valuation of benefits.

Report methods

The systematic review will be undertaken following the general principles outlined in NHS CRD Report 4 (2nd edition).

This research protocol may be updated as the research programme progresses. Any changes in the protocol will be notified and agreed with the National Coordinating Centre for Health Technology Assessment (NCCHTA).

Search strategy

Electronic databases that will be searched include: Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, NHS CRD (University of York), Database of Abstracts of Reviews of Effective (DARE), NHS Economic Evaluations Database (EED) and HTA databases, MEDLINE (Silverplatter), PubMed, EMBASE, National Research Register, Science Citation Index, BIOSIS, EconLit, Medical Research Council (MRC) Trials database, Early Warning System, and Current Controlled Trials. These will be searched for the

periods covered by the databases up until September 2002 and will be limited to English language.

Bibliographies of related papers will be assessed for relevant studies.

Experts will be contacted for advice and peer review, and to identify additional published and unpublished references and any currently ongoing studies.

Inclusion and exclusion criteria

Interventions will include (1) traditional surgery debulking resection of all gross disease, (2) cytoreductive surgery combined with chemotherapy, and (3) the Sugarbaker procedure defined as cytoreductive surgery combined with heated adjuvant IPEC. Other proposed treatment options such as no active treatment, treatment with radiotherapy using isotope implantation, mucolytic agents (such as saline or dextrose) as an aid to operative cytoreduction for obtaining closed catheter drainage of mucinous material for palliation, and phototherapy as an adjuvant to conventional dissection at laparotomy will be excluded.

Participants will include those people who are diagnosed as having PMP characterised by histologically benign peritoneal tumours with indolent course originating in the appendix. Importantly, it will not include aggressive carcinomas (e.g. mucinous carcinoma of the appendix) or malignant adenocarcinomas that metastasise through the lymphatic or blood system (e.g. peritoneal carcinomatosis). Also excluded are mucinous low-malignant-potential tumours and carcinomas of ovarian origin, which are thought to represent secondary involvement to perforated mucinous adenoma of appendix. Studies considering the effectiveness of interventions for tumours without specific mention of PMP or that include other conditions with PMP when reporting aggregate outcomes will be excluded.

Although the search will attempt to find evidence at the higher levels of the hierarchy of evidence, it is unlikely, owing to the rarity of the condition that there will be any experimental studies. As such, the primary focus of the systematic review will be on identifying systematic reviews and observational studies, specifically case series. As a consequence, any comparisons made will be indirect, necessitating close scrutiny of sources of confounding and bias. If uncontrolled studies, particularly case series, provide the evidence for assessing clinical effectiveness, additional evidence on the natural history of the condition will be sought. Economic evaluations will be included if they include a comparator and both costs and consequences or if they are costing studies.

Studies will be included if they report survival, recurrence or quality of life as primary outcomes and complications as secondary outcome at a minimum of 2 years' follow-up. Treatment for PMP is often beneficial for survival and recurrence when assessed in the short term (5 years or less), so to be considered effective interventions should be assessed over the longer term of 10 years.

Inclusion criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Data extraction strategy

Data will be extracted by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Quality assessment strategy

The quality of included systematic reviews will be assessed using criteria recommended by NHS CRD (University of York), while case series will be judged using criteria recommended by NHS CRD (see Appendix 5). Quality of economic evaluations will be assessed for their internal validity (i.e. the methods used) using a standard checklist, and external validity (i.e. the generalisability of the economic study to the population of interest) using a series of relevant questions (see Appendix 6).

Quality criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Methods of analysis/synthesis

Clinical effectiveness will be synthesised through a narrative review with full tabulation of results of all included studies. Subgroup analyses by treatment type and patient group will be undertaken where possible, to allow guidance on targeting treatment to people most likely to benefit. If appropriate, a meta-analysis will be considered.

Methods for estimating quality of life, costs and cost-effectiveness and/or cost/quality-adjusted life-years

Cost-effectiveness will be assessed by a two-stage procedure. First, a narrative review of published economic evaluation studies will be synthesised. The second stage will be to adapt an existing cost-effectiveness model or construct a new one using the best available evidence to determine cost-effectiveness in a UK setting.

To determine applicability and resource implications to the NHS, resources and costs will be sought from published UK sources (e.g. British National Formulary or published studies) and where appropriate and available, local NHS.

Effectiveness data, in terms of the outcomes described in the above section, will be extracted from published trials and used in association with the cost data to obtain measures of cost-effectiveness. If available, quality of life information will be obtained from the literature or other sources to calculate cost-utility estimates in terms of cost per quality-adjusted life-year (QALY). The robustness of the results to the assumptions made in the model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis. If comparative data on clinical effectiveness are unavailable, a costing study will be undertaken.

Appendix 3

Sources of information, including databases searched and search terms

The flowchart for the identification and inclusion of studies for the assessment of clinical effectiveness is shown in *Figure 2* and that for economic evaluations in *Figure 3*.

The databases in *Table 12* were searched for published studies, and recently completed and ongoing research.

Clinical effectiveness searches

The following strategy was used to search MEDLINE and the Cochrane Library.

Pseudomyxoma or peritoneal adenomucinosi ((pseudomyxoma) or (periton* near adenomucinosi)) and (English in la)

The publication types of letters or editorials were excluded.

The above strategy was adapted as appropriate for the remaining databases shown in *Table 12*. The details of all search strategies used are available on request.

Cost-effectiveness and quality of life searches

The following keywords were used to search the databases shown below:

((costs OR cost OR costed OR costing OR economic* OR price* OR (quality AND life) OR wellbeing OR well-being)) AND ((pseudomyxoma) or (periton* near adenomucinosi))

Additional searching

Bibliographies: All references of articles for which full papers were retrieved were checked to ensure that no eligible studies had been missed.

TABLE 12 Databases searched

| Databases searched | Date or issue of search |
|--|--|
| Cochrane Library (all sections) | 2002 issue 2 |
| MEDLINE (SilverPlatter) | 1966 – 5 May 2002 week 2 |
| EMBASE (SilverPlatter) | 1980 – June 2002 |
| PubMed (Internet version) | 1 May – all database 29 May 2002 – last 180 days 22 July 2002 – last 60 days |
| Science and Social Sciences Citation Index | 2000–2002 |
| CancerLit | Database |
| Web of Science Proceedings | Database |
| BIOSIS | 2000–2002 |
| National Research Register | 2002 issue 2 |
| Current controlled trials | 30 May 2002 |
| Clinical Trials.gov | 30 May 2002 |
| NCI Cancer Trials | 30 May 2002 |

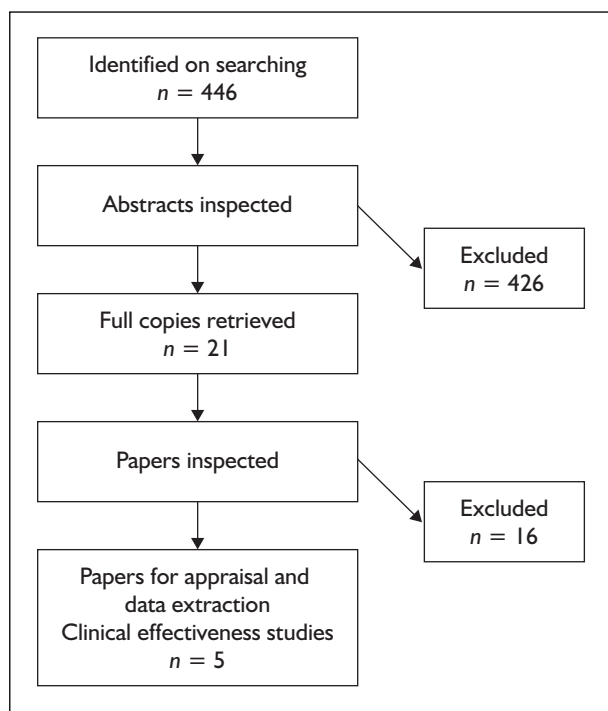


FIGURE 2 Flowchart of identification of case series for clinical effectiveness systematic review

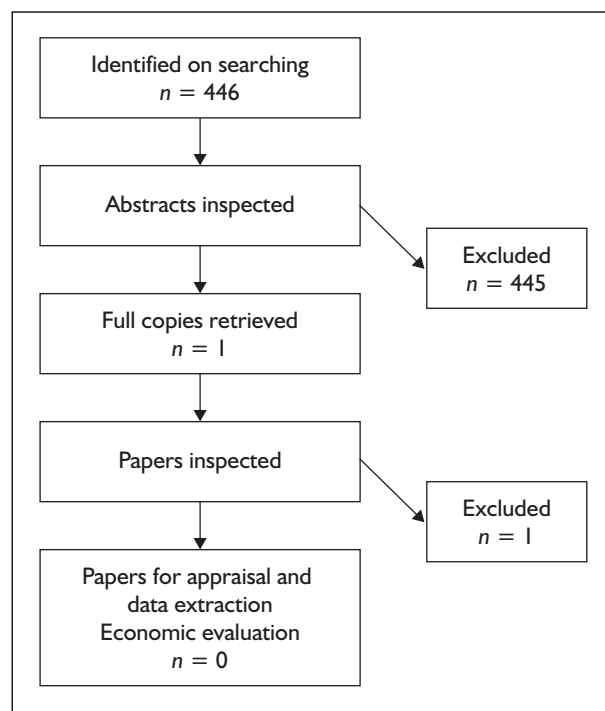


FIGURE 3 Flowchart of identification and inclusion of economic evaluation papers

Appendix 4

List of excluded clinical effectiveness studies

- Averbach AM, Sugarbaker PH. Recurrent intraabdominal cancer causing intestinal obstruction: Washington Hospital Center experience with 42 patients managed by surgery and intraperitoneal chemotherapy. *Cancer Treat Res* 1996;**81**:133–47. (Not PMP of appendiceal origin.)
- Butterworth SA, Panton NM, Klasson DJ, Shah AM, McGregor GI. Morbidity and mortality associated with intraperitoneal chemotherapy for pseudomyxoma peritonei. *Am J Surg* 2002;**183**:529–32. (Mixed subgroups by histology.)
- Esquivel J, Sugarbaker PH. PMP in a hernia sac: analysis of 20 patients in whom mucoid fluid was found during a hernia repair. *Eur J Surg Oncol* 2001;**27**:54–8. (No outcomes.)
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Appendix 5

Quality criteria for assessment of case series (NHS CRD, University of York)

- Is the study based on a representative sample selected from a relevant population?
 - Are the criteria for inclusion explicit?
 - Did all individuals enter the survey at a similar point in their disease progression?
 - Was follow-up long enough for important events to occur?
- Were outcomes assessed using objective criteria or was blinding used?
 - If comparisons of subseries were being made, was there sufficient description of the series and the distribution of prognostic factors?

Appendix 6

Quality assessment of economic evaluations

Internal validity of studies

| Item | Study |
|--|-------|
| <ol style="list-style-type: none"> 1. Well-defined question 2. Clear description alternatives 3. Reasonable study type 4. Effectiveness established 5. Estimates related to population risks 6. Relevant costs and consequences identified <ul style="list-style-type: none"> • Healthcare resources (adverse events) • Patient/family resources • Social care sector resources • Patient benefits • Carer benefits 7. Costs and consequences measured accurately 8. Costs and consequences valued credibly 9. Differential timing considered 10. Incremental analysis performed 11. Sensitivity analysis performed 12. Modelling conducted reasonably | |
| <p>?, unclear or unknown. ✓, item included or judged to have acceptable internal validity. X, factor not included or judged to have unacceptable internal validity.</p> | |

External validity of studies

| Item | Study |
|---|-------|
| <ol style="list-style-type: none"> 1. Patient group Are the patients in the study similar to those of interest in England and Wales? 2. Healthcare system/setting <ul style="list-style-type: none"> • Comparability of available alternatives? • Similar levels of resources? • No untoward supply constraints? • Institutional arrangements comparable? 3. Treatment <ul style="list-style-type: none"> • Comparability with clinical management? 4. Resource costs <ul style="list-style-type: none"> • Comparability between study and setting/population of interest? 5. Marginal versus average costs <ul style="list-style-type: none"> • What difference does this make? • Are there real cost savings? | |
| <p>?, unclear or unknown. ✓, judged item suitable to generalise to England and Wales with or without some readjustment. X, factor judged not suitable to generalise to England and Wales; either not possible to see how an adjustment could be made easily in short/medium term, or relevant data unavailable.</p> | |

Appendix 7

Summary of evidence of effectiveness of the Sugarbaker procedure for the treatment of PMP

| Reference and design | Intervention | Subjects | Outcome measures |
|--|---|---|---|
| Ronnett <i>et al.</i> , 2001 ⁶ USA Case series | <p>Treatment: Series of peritonectomy procedures and organ resections maximally to debulk (cytoreduce) tumour. In early postoperative period (postoperative days 1–6), chemotherapeutic agents (MMC and 5-FU) instilled into peritoneal cavity. Subsequently, three adjuvant cycles of systemic MMC and intraperitoneal 5-FU administered. All patients were treated by the same surgeon, in the same way</p> <p>Other interventions used: None indicated</p> | <p>N = 109 with PMP DPAM = 65 (60%) PMCA = 30 (28%) PMCA-I = 11 (10%) PMCA-D = 3 (3%)</p> <p>Characteristics of target population: Patients diagnosed with PMP or mucinous adenocarcinoma with multifocal peritoneal involvement; surgically treated by one of the study authors (P. Sugarbaker) between 1983 and 1993; peritoneal and serosal surfaces of the abdomen and pelvis were involved by lesions containing pools of dissecting mucin associated with fibrosis with or without epithelial cells</p> <p>Exclusion criteria: Patients with minimal sampling of the peritoneal lesions, minimal extracellular mucin in the peritoneal lesions or lesions confined to the right lower quadrant</p> <p>Participants: Characterised into one of three groups (DPAM, PMCA or PMCA-I/D) based on pathological features of peritoneal lesions: DPAM = 62% men, 38% women, mean age 49.1 years PMCA = mean age 47.1 years PMCA-I/D = mean age 47.5 years</p> | <p>Outcome measures: Survival (5- and 10-year rates), mortality and disease status at end of follow-up</p> <p>Method of assigning outcomes: Not available</p> <p>Length of follow-up: Mean: DPAM = 95.7 months PMCA = 27.2 months PMCA-I/D = 57.9 months Median: DPAM = 104.0 months PMCA = 16.0 months PMCA-I/D = 50.5 months</p> |
| <p>Results</p> <ul style="list-style-type: none"> • Survival (mean months): 112.4 vs 26.5 vs 46.2 (all results DPAM, PMCA and PMCA-I/D, respectively) • Survival (median months): Not calculated since > 50% of patients alive at end of follow-up vs 16.0 vs 50.5 • Survival (5-year rate): 75% vs 14% vs 50% ($p = 0.0001$, PMCA, PMCA-I/D vs DPAM) • Survival (10-year rate): 68% vs 3% vs 21% ($p = 0.0001$, PMCA, PMCA-I/D vs DPAM) • Mortality: 20 (30.8%) vs 28 (93.3%) vs 11 (78.6%) • Status of those alive: NED = 34/40 (85%) vs 1/30 (3%) vs 1/3 (33.3%), AWD = 6/40 (15%) vs 0 (0%) vs 1/3 (33.3%) • Patients who died of other causes: 5/20 (25%) vs 0/28 (0%) vs 1/11 (9%) • One patient from PMCA lost to follow-up, one PMCA-I/D patient data missing • No complication data available | | | |
| | | | <i>continued</i> |

Methodological comments

- *Representative sample*: No indication of representativeness of sample provided. Individuals were diagnosed with PMP or mucinous adenocarcinoma with multifocal peritoneal involvement identified from a review of the patient file of one of the study authors who surgically treated the patients from 1983 to 1993
- *Inclusion criteria of sample*: No a priori inclusion criteria stated
- *Comparability of sample disease status*: All patients were diagnosed into three groups: DPAM, PMCA or PMCA-I/D. Disease description comprehensive
- *Adequacy of follow-up*: Follow-up information available for 108 of 109 patients. Mean follow-up (months) of 95.7 vs 27.2 vs 57.9, DPAM, PMCA and PMCA-I/D, respectively.
- *Objective criteria and blinding of outcome assessment*: No blinding carried out, unsure of outcome assessment criteria used
- *Representative subgroups*: No subgroup analysis performed
- *Statistical analysis*: All statistical analyses performed with SAS software (SAS Institute, USA). Ranges and frequency distributions of all continuous and categorical variables examined. ANOVA test used to compare mean differences in age in three groups. Chi-squared test used to compare the number of deaths in each group. Patient survival analysed according to Kaplan–Meier method, with death due to disease as the end-point. Statistical significance was tested by log-rank statistics. Reviewer calculated percentage for status

General comments

- *Outcome measures*: Survival (mean/median and rates, 5 and 10 years), follow-up, mortality and disease status
- *Intercentre variability*: Single centre
- *Conflicts of interest*: No funding information provided

Quality assessment for case series

| Question | Answer |
|--|---------|
| Is the study based on a representative sample selected from a relevant population? | No |
| Are the criteria for inclusion explicit? | No |
| Did all individuals enter the survey at a similar point in their disease progression? | Unclear |
| Was follow-up long enough for important events to occur? | Unclear |
| Were outcomes assessed using objective criteria or was blinding used? | Unclear |
| If comparisons of subseries are being made, was there sufficient description of the series and the distribution of prognostic factors? | NA |

| Reference and design | Intervention | Subjects | Outcome measures | | | | | | | | | | | | | | |
|--|---|---|---|----------|--------|--|----|--|----|---|---------|--|---------|---|---------|--|----|
| Smith <i>et al.</i> , 1992 ¹² USA Case-series | <p>Treatment arms: Cytoreductive procedures carried out on all patients. Nine patients underwent single debulking; eight underwent multiple debulking. Ten were treated with chemotherapy (four with intraperitoneal and six with intravenous chemotherapy)</p> <p>Other interventions used: Not stated</p> | <p>Number of patients: $N = 17$</p> <p>Characteristics of target population: Patients with a clinical and pathological diagnosis of malignant PMP were treated at Memorial Sloan-Kettering Cancer Centre during 1952–1989, identified as being of appendiceal origin</p> <p>Exclusion criteria: None stated</p> <p>Participants: Mean age 52 (28–68) years; 65% men; 82% white</p> | <p>Outcome measures: Survival rate, presenting symptoms and duration, debulking and status, and complications.</p> <p>Method of assigning outcomes: None stated</p> <p>Length of follow-up: Mean follow-up 62 (4–120) months</p> | | | | | | | | | | | | | | |
| <p>Results</p> <ul style="list-style-type: none"> • Survival rates (actuarial): 75% and 60%, for 5 and 10 years, respectively • Survival rate range: 21 months to 12 years, postoperatively • No significant difference in survival according to gender or age of patient • Presenting symptoms: abdominal distension 6 (35%), hernia 5 (29%), abdominal pain 3 (18%), palpable mass 2 (12%), anaemia 1 (6%) • Average duration of symptoms (months): abdominal distension (16), hernias (16), mass (16), abdominal pain (2) • Status: NED = 7/17 (41.2%), AWD = 6/17 (35.3%), DOD = 4/17 (23.5%). Five of NED have been clinically disease free since initial operation; two underwent a second debulk • Multiple debulking: 8/17 (47%). Of those with multiple debulking: NED = 2/8 (25%), AWD = 2/8 (25%) (one alive 57 months after first operation with two additional debulking operations, and one alive 10 years after first operation with five additional debulks), DOD = 4/8 (50%) (average survival 50 months) • Difference in survival between single and multiple debulking is not statistically significant • Postoperative chemotherapy: NED = 3/10 (30%), AWD = 4/10 (40%), DOD = 3/10 (30%); (second) NED = 0/3 (0%), AWD = 1/3 (33.3%), DOD = 2/3 (66.7%) • No significant difference between those treated with operations alone and those who received chemotherapy • Average hospital stay was 15 days, due primarily to prolonged ileus • Complications: Starch peritonitis ($n = 1$) treated with repeat laparotomy and hospitalised for 47 days <p>Methodological comments</p> <ul style="list-style-type: none"> • Representative sample: Not able to ascertain. Patients with a clinical and pathological diagnosis of malignant PMP were treated at Memorial Sloan-Kettering Cancer Centre during 1952–1989, identified as being of appendiceal origin • Inclusion criteria of sample: No a priori inclusion criteria stated • Comparability of sample disease status: Patients diagnosed with malignant PMP of appendiceal origin • Adequacy of follow-up: Follow-up of all patients. Mean 62 months • Objective criteria and blinding of outcome assessment: No blinding, mortality is an objective outcome assessment • Representative subgroups: No sub-group analysis used • Statistical analysis: Reviewer calculated percentage for 'presenting symptoms'. NED, AWD and DOD data aggregated by reviewer. Kaplan–Meier survival curves calculated. No p-values given for comparison <p>General comments</p> <ul style="list-style-type: none"> • Outcome measures: Survival rates, presenting symptoms, average duration of symptoms, status and complications • Intercentre variability: Single centre • Conflicts of interest: None mentioned | | | | | | | | | | | | | | | | | |
| <p>Quality assessment for case series</p> <table border="1"> <thead> <tr> <th>Question</th> <th>Answer</th> </tr> </thead> <tbody> <tr> <td>Is the study based on a representative sample selected from a relevant population?</td> <td>No</td> </tr> <tr> <td>Are the criteria for inclusion explicit?</td> <td>No</td> </tr> <tr> <td>Did all individuals enter the survey at a similar point in their disease progression?</td> <td>Unclear</td> </tr> <tr> <td>Was follow-up long enough for important events to occur?</td> <td>Unclear</td> </tr> <tr> <td>Were outcomes assessed using objective criteria or was blinding used?</td> <td>Unclear</td> </tr> <tr> <td>If comparisons of subseries are being made, was there sufficient description of the series and the distribution of prognostic factors?</td> <td>NA</td> </tr> </tbody> </table> | | | | Question | Answer | Is the study based on a representative sample selected from a relevant population? | No | Are the criteria for inclusion explicit? | No | Did all individuals enter the survey at a similar point in their disease progression? | Unclear | Was follow-up long enough for important events to occur? | Unclear | Were outcomes assessed using objective criteria or was blinding used? | Unclear | If comparisons of subseries are being made, was there sufficient description of the series and the distribution of prognostic factors? | NA |
| Question | Answer | | | | | | | | | | | | | | | | |
| Is the study based on a representative sample selected from a relevant population? | No | | | | | | | | | | | | | | | | |
| Are the criteria for inclusion explicit? | No | | | | | | | | | | | | | | | | |
| Did all individuals enter the survey at a similar point in their disease progression? | Unclear | | | | | | | | | | | | | | | | |
| Was follow-up long enough for important events to occur? | Unclear | | | | | | | | | | | | | | | | |
| Were outcomes assessed using objective criteria or was blinding used? | Unclear | | | | | | | | | | | | | | | | |
| If comparisons of subseries are being made, was there sufficient description of the series and the distribution of prognostic factors? | NA | | | | | | | | | | | | | | | | |

| Reference and design | Intervention | Subjects | Outcome measures |
|---|---|---|---|
| Sugarbaker <i>et al.</i> , 1993 ¹³ USA Case series | Treatment: Cytoreductive surgery (five peritonectomy procedures) by Sugarbaker as described elsewhere and in the paper, followed by intraperitoneal chemotherapy described in the paper Other interventions used: Not reported | Number of patients and controls: PMP = 38 (subset of study) Characteristics of target population: Patients with histologically proven peritoneal carcinomatosis from appendiceal cancer treated between September 1981 and January 1992. Patients were diagnosed as PMP, cystadenocarcinoma after review of surgical findings and histopathologic sections Exclusion criteria: Not reported Participants: (of total study – not given for PMP): 66.7% males; age (median) 51 (28–77) years; 38/69 (55.1%) patients identified as PMP, 25/69 (36.2%) cystadenocarcinoma, 6/69 (8.7%) adenocarcinoma | Outcome measures: Survival disaggregated into PMP, cystadenocarcinoma, adenocarcinoma Method of assigning outcomes: Not reported Length of follow-up: Not reported |
| Results | | | |
| <ul style="list-style-type: none"> • Survival (3-year rate): 89.5% for PMP | | | |
| Methodological comments | | | |
| <ul style="list-style-type: none"> • <i>Representative sample:</i> Not able to ascertain. Individuals were diagnosed with histologically proven peritoneal carcinomatosis from appendiceal cancer treated between September 1981 and January 1991 • <i>Inclusion criteria of sample:</i> No a priori inclusion criteria stated • <i>Comparability of sample disease status:</i> Patients were diagnosed as PMP after surgical findings and review of histopathological sections • <i>Adequacy of follow-up:</i> Follow-up length not reported • <i>Objective criteria and blinding of outcome assessment:</i> No blinding carried out, unsure of outcome assessment • <i>Representative subgroups:</i> No subgroup analysis used • <i>Statistical analysis:</i> Not reported | | | |
| General comments | | | |
| <ul style="list-style-type: none"> • <i>Outcome measures:</i> Survival (3-year) • <i>Intercentre variability:</i> Single-centre • <i>Conflicts of interest:</i> None mentioned | | | |
| Quality assessment for case series | | | |
| Question | | | Answer |
| Is the study based on a representative sample selected from a relevant population? | | | No |
| Are the criteria for inclusion explicit? | | | No |
| Did all individuals enter the survey at a similar point in their disease progression? | | | Unclear |
| Was follow-up long enough for important events to occur? | | | Unclear |
| Were outcomes assessed using objective criteria or was blinding used? | | | Unclear |
| If comparisons of subseries are being made, was there sufficient description of the series and the distribution of prognostic factors? | | | NA |

| Reference and design | Intervention | Subjects | Outcome measures |
|---|--|--|---|
| Sugarbaker, 2001 ¹⁰ USA Case series | Cytoreduction plus (1) i.v. chemotherapy, starting with MMC for patients left with gross disease (2) perioperative HIPEC (MMC) for patients with adenomucinosi s (3) HIPEC and 5 days of IPEC 5-FU for patients with mucinous adenocarcinoma or PMP/adenocarcinoma hybrid | PMP: $n = 385$ Setting: Hospital | Survival Mortality Morbidity (complications) Follow-up: mean 37.6 months |
| Results | | | |
| <i>Survival at 3 years (Kaplan–Meier survival curves)</i> | | | |
| 1. By completeness of cytoreduction | | | |
| (defined by size of unresected tumour nodules remaining): | | | |
| CC0 = nodules not visible | | | |
| CC1 = complete cytoreduction, nodules < 0.25 cm | | | |
| CC2 = incomplete cytoreduction, nodules ≥ 0.25 and ≤ 2.5 cm | | | |
| CC3 = incomplete cytoreduction, nodules > 2.5 cm | | | |
| <ul style="list-style-type: none"> • complete cytoreduction (CC0 and CC1, $n = 250$) 0.9 • incomplete cytoreduction (CC2 and CC3, $n = 135$) 0.35 | | | |
| Data from graph, $p < 0.0001$. No significant differences between CC2 and CC3 | | | |
| 2. By histology | | | |
| (defined as adenomucinosi s, hybrid adenomucinosi s + mucinous adenocarcinoma, or mucinous adenocarcinoma): | | | |
| <ul style="list-style-type: none"> • adenomucinosi s ($n = 224$) 0.88 • Hybrid + adenocarcinoma ($n = 161$) 0.42 | | | |
| Data from graph, $p = 0.0001$. No significant differences between patients with intermediate type and mucinous adenocarcinoma | | | |
| 3. By PSS | | | |
| (defined as | | | |
| PSS 0 = biopsy only | | | |
| PSS 1 = exploratory laparotomy, 1–2 regions | | | |
| PSS 2 = exploratory laparotomy with some resections, 2–5 regions (greater omentectomy or greater omentectomy plus a right colectomy) | | | |
| PSS 3 = attempted complete cytoreduction, > 5 regions (greater omentectomy, right colectomy, hysterectomy and bilateral salpingo-oophorectomy) | | | |
| <ul style="list-style-type: none"> • PSS 0–2 ($n = 248$) 0.8 • PSS 3 ($n = 119$) 0.65 | | | |
| Data from graph, $p = 0.001$. (data on 18 patients not available) | | | |
| <i>Survival analysis by Cox semiparametric model</i> | | | |
| <ul style="list-style-type: none"> • Risk ratio of complete versus incomplete cytoreduction was 9.98 (95% confidence interval 4.23–23.09) • Complete cytoreduction and adenomucinosi s by pathology 5-year survival 86%; hybrid pathology survival 50% at 5 years (from abstract; not supported by graphs or data) • Incomplete cytoreduction had 5-year survival of 20%, and 0% at 10 years (from abstract, not supported by graphs or data) | | | |
| <i>Morbidity and mortality of 155 consecutive patients treated in 1998 and 1999</i> | | | |
| <ul style="list-style-type: none"> • Mortality: 2% • Major complications: pancreatitis (7.1%) and fistula formation (4.7%); anastomotic leaks 2.4% • Grade III/IV morbidity: 27% | | | |
| Methodological comments | | | |
| <ul style="list-style-type: none"> • <i>Representative sample:</i> Patients are all those treated before 1999 (presumably at institute of affiliation) with adenomucinosi s, mucinous adenocarcinoma or pseudomyoma/adenocarcinoma hybrid and mucinous carcinomatous, so therefore includes disease groups not strictly representative of target population. Not described as representative • <i>Inclusion criteria of sample:</i> No inclusion criteria specified | | | |
| | | | <i>continued</i> |

Methodological comments (cont'd)

- *Comparability of sample disease status*: During the period under consideration there were changes in surgery (more extensive) and chemotherapy (route and timing). Also patient selection changed
- *Adequacy of follow-up*: Mean 37.6 months. Complete follow-up except for PSS results
- *Objective criteria and blinding of outcome assessment*: Some objective criteria used, but no mention of blinding for others
- *Representative subgroups*: Data analysed according to significant prognostic variables
- *Statistical analyses*: No overall data summary, data presented in graph form only. Kaplan–Meier survival curves, with log-rank test for comparison, *p*-values for each analysis

General comments

- *Outcome measures*: Survival and mortality appropriate
- *Intercentre variability*: Single centre
- *Conflict of interests*: No information

Quality assessment for case series

| Question | Score |
|--|---------|
| Is the study based on a representative sample selected from a relevant population? | No |
| Are the criteria for inclusion explicit? | No |
| Did all individuals enter the survey at a similar point in their disease progression? | No |
| Was follow-up long enough for important events to occur? | Unclear |
| Were outcomes assessed using objective criteria or was blinding used? | Unclear |
| If comparisons of subseries are being made, was there sufficient description of the series and the distribution of prognostic factors? | No |

| Reference and design | Intervention | Subjects | Outcome measures |
|--|---|---|--|
| Witkamp <i>et al.</i> , 2001 ¹¹ Netherlands Case series | Extensive surgical cytoreduction (to leave no macroscopic tumour or deposits < 2.5 mm in diameter) + HIPEC with mitomycin (MMC, 15–40 mg/m ² , intraperitoneal temperature 40–41°C, perfusion for 90 minutes) Adjuvant 5-FU (400 mg/m ²) and leucovorin (80 mg/m ²) if malignant disease, for 6 months or until progression of tumour observed or intolerable toxicity occurred GP visits 6 weeks and 3 months postdischarge and then at 3-monthly intervals | PMP: <i>N</i> = 46 (19 male, 27 female) Characteristics of target population: Diagnosis proven by histological or cytological examination; no sign of distant metastases on CT of abdomen and chest; tumour technically respectable; patient medically fit to undergo major surgery Participants: Mean age: 57 years (range 34–76) years; 21 with recurrent disease; 41 had prior operations, mean laparotomies 2 (range 1–5); 7 had previous systemic chemotherapy; 1 pretreated with intraperitoneal cisplatin; 2 had previous radiotherapy Setting: hospital | Survival Mortality Recurrence Morbidity (complications) MMC toxicity CEA Follow-up: Median 12 (range 1–43) months |
| Results | | | |
| <ul style="list-style-type: none"> Tumour distribution recorded for seven abdominal areas (left and right subdiaphragmatic, subhepatic, omentum/transverse colon, small intestine/mesentery, ileocaecal and pelvic): <ul style="list-style-type: none"> – 33 subjects had tumour spread over 5 or more regions – 10 had tumour limited to 2–4 abdominal regions – 3 subjects had tumour in 1 abdominal region Optimal surgical cytoreduction: achieved in 40 subjects MMC dosage: 15 mg/m² in 1 patient, 30 mg/m² in 2, 35 mg/m² in 38, 40 mg/m² in 5. Perfusion for 90 minutes in all but 1 patient (60 minutes) Mean hospital stay: 31 (range 16–146) days Major complications related to surgery: in 18 patients Morbidity rate: 39% (stomach or bowel perforation <i>n</i> = 10, enteral fistula <i>n</i> = 6, pancreatitis <i>n</i> = 1, pulmonary embolism <i>n</i> = 3, peripheral pressure neuropathy <i>n</i> = 5, pneumonia <i>n</i> = 3, intra-abdominal or wound abscess <i>n</i> = 4) Reoperation for postoperative complications: 11 patients In-hospital mortality rate: 9% (4/46) Causes of death: septic shock (<i>n</i> = 3), sudden death probably due to pulmonary embolism (<i>n</i> = 1) One patient developed multiple and persistent enteral fistulae requiring multiple bowel resections, resulting in short bowel syndrome MMC toxicity (WHO Common Toxicity Criteria): bone-marrow suppression, grade 1/2 leucocytopenia in 12 patients, grade 3/4 in 10 patients. Thrombocytopenia in 4 patients. No nephrotoxicity or cardiotoxicity Adjuvant chemotherapy: 22 patients received 5-FU; stopped in 5 owing to intolerable toxicity (<i>n</i> = 4) or disease progression (<i>n</i> = 1). Survival after median follow-up: 40/46 (87%) Local recurrence: in 8/46 patients (17%) Mean interval between HIPEC and recurrence: 13 months Mortality: recurrent disease 26 months after HIPEC (<i>n</i> = 1); unrelated causes (<i>n</i> = 1) Actuarial survival rate (Kaplan-Meier): 91% at 2 years, 81% at 3 years | | | |
| Methodological comments | | | |
| <ul style="list-style-type: none"> Representative sample: First series of patients with PMP treated with aggressive maximal surgery and HIPEC at centre. No methods and not described as representative of target population Inclusion criteria of sample: Stated Comparability of sample disease status: Patients at different stages of disease and treatment Adequacy of follow-up: Short term, median 12 (range 1–43) months. All patients followed up Objective criteria and blinding of outcome assessment: Some objective criteria used; no blinding described for other outcomes Representative subgroups: No subgroup analysis Statistical analyses: Survival after median follow-up given, and actuarial survival rate | | | |
| | | | <i>continued</i> |

| | |
|---|--------------|
| General comments | |
| <ul style="list-style-type: none"> • <i>Outcome measures</i>: Survival, mortality, recurrence appropriate • <i>Intercentre variability</i>: Single centre • <i>Conflict of interests</i>: No information | |
| Quality assessment for case series | |
| Question | Score |
| Is the study based on a representative sample selected from a relevant population? | Unclear |
| Are the criteria for inclusion explicit? | Yes |
| Did all individuals enter the survey at a similar point in their disease progression? | No |
| Was follow-up long enough for important events to occur? | No |
| Were outcomes assessed using objective criteria or was blinding used? | Unclear |
| If comparisons of subseries are being made, was there sufficient description of the series and the distribution of prognostic factors? | NA |
| ANOVA: analysis of variance; PSS: prior surgical score. | |

Appendix 8

Cost for Sugarbaker procedure for PMP

| Cost area | | Cost per hour | Comment |
|---------------------------|---|---------------|--|
| Medical staff | | | |
| Consultant | With discretionary points | £46.35 | Experienced medical staff who are eminent in their field can be awarded distinction awards. |
| Consultant | Without discretionary points | £33.83 | |
| Specialist registrar | | £17.35 | The final trainee grade for medical staff: these staff are likely to assist at complex operations and may undertake more routine ones themselves |
| Anaesthetists | | £33.83 | This would be a member of the medical staff, not normally nurse anaesthesiologists in the UK. The anaesthetist would be present throughout the operation to oversee the welfare of the patient; in addition, he or she would be present for a minimum of 15 minutes before the operation to anaesthetise the patient (the precise time would depend on the health of the patient). The grade of anaesthetist may vary; therefore, using the rate for a consultant without discretionary points would be a reasonable average |
| Nursing staff | | | |
| Theatre practitioner | Trained nurse, equivalent to grade E nurse | £11.30 | For an operation of this type, there would be at least two trained nurses and an auxiliary nurse |
| Auxiliary nurse | Grade A nurse | £6.17 | |
| Theatre costs | | | |
| Cost per theatre minute | Surgical theatres | £1.04 | This cost per minute excludes all staff costs |
| | | £3.58 | Cost per minute including nursing and support staff but not medical staff |
| Theatres equipment | | | |
| Unavailable | | | There is likely to be usage of other instruments, and medical and surgical supplies and equipment, in addition to the staplers, which often come in standard packs |
| Intensive care | | | |
| Cost per bed-day | Direct costs only, excluding medical staff time | £1063 | With an operation of this length, a patient would transfer directly into intensive care without spending time in theatre recovery Cost is for stay in general ICU |
| | Direct costs plus medical staff costs | £1127 | |

continued

| Cost area | Cost per hour | Comment |
|--|--------------------|---|
| Ward stay | | |
| Cost per bed-day | £118 | This is the direct cost of staying on a surgical ward. It includes nursing staff and non-staff costs but not medical staff time. It is also an average and does not take into account a higher than average dependency |
| Cost per bed-day including medical staff costs | £154 | The above, plus medical staff time. This is probably overstated because some of those medical staff costs would relate to time undertaking operations in theatre. The above does not include usage of pathology, radiology and other diagnostic or paramedic services which are likely to be part of a patient's care |
| Home stay | | |
| Unavailable | | |
| Follow up care | | |
| Unavailable | | |
| CT scan | CT scan on abdomen | £59 |
| NB. All staff costs include NI and superannuation, but not any additional payments relating to shift work. | | |



Health Technology Assessment Programme

Prioritisation Strategy Group

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We look forward to hearing from you.